

A TREATISE
on the
ETIOLOGY, PATHOLOGY, DIAGNOSIS and TREATMENT
OF SYPHILIS.

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by

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PART I. INTRODUCTION.

My object in this Thesis is to describe the principal factors leading up to our present knowledge of Syphilis.

Since the beginning of the summer of 1908 I have devoted a considerable amount of time in studying the subject from a theoretical as well as a practical aspect.

I am greatly indebted to Geheimrath Professor A. Neisser of Breslau for his kindness in admitting me to his klinik as a regular assistant, and for the knowledge and experience gained by association with him and Professors Brück and Schäffer his chief assistants, during the three years I spent at the Klinik.

Such information and experience as I have gained in the laboratory, wards and library of Professor Neisser's Klinik I shall incorporate in my Thesis.

The principal aim of medical science is to endeavour to alleviate the sufferings of humanity, and wherever possible to effect a cure.

In no branch of medicine in recent years have greater advances been made than in this important question of the treatment of Syphilis. Within the comparatively short period of ten years, our knowledge of the disease, and especially our knowledge of how to treat it, has advanced remarkably; whilst there is every reason to believe that further progress is sure to follow.

The modern treatment of Syphilis is based upon three great discoveries.

- i. The discovery of the *Spirochaeta pallida* by Schandinn.
- ii. The discovery by Metschnikoff and Roux that apes are susceptible to inoculation with the virus of Syphilis.
- iii. The discovery by Bordet and Gengon of the fixation of complement reaction introduced for the diagnosis of syphilis by Wassermann, Neisser and Brück.

PART II. ETIOLOGY.

SECTION I.

Discovery of the spirochaeta pallida.

On the 3rd March 1905 Fritz Schaudinn⁽¹⁾ in collaboration with Erich Hoffmann discovered the *Spirochaeta pallida*. u/

They found it first in the serum from a genital papule. Further publications⁽²⁾ in April and May demonstrated the presence of the organism in the depth of the tissues, in lymphatic glands and from spleno-puncture as well as in primary sores and secondary lesions.

They described two kinds of *Spirochaetes*, the one remarkably delicate, feebly refractive, characterised by steep and narrow undulations and staining badly; the other spirochaete was much thicker, strongly refractive, characterised by more flattened and wider undulations and staining more readily and intensely.

This second type named *Sp. refringens*.

They emphasised the corkscrew like form and greater fineness of the *Sp. pallida* as well as its paleness in staining.

Identification of the organism in lesions
and organs of the human species.

Schandinn sent some preparations to Metschnikoff and Roux (3) of the Institut Pasteur with the request that they might attempt to prove the presence of *Sp. pallida* in the case of experimental syphilis with apes. These observers demonstrated the presence of *Sp. pallida* in primary sores of chimpanzee and macacus, as well as in unbroken papules on the human body far removed from the genitals.

Levadit~~z~~ (4) showed the presence of *Sp. pallida* in internal organs (lung, liver and spleen) and in the bullae of bullous syphiloderm.

Hoffmann (5) examined an undoubted case of congenital syphilis which died 10 hours after birth, and demonstrated the presence of *Sp. pallida* in skin lesions, lymphatics, liver and spleen.

Since these primary discoveries the *Sp. pallida* has been found in all types of syphilitic lesions, in all organs and fluids of the body of hereditary syphilitic foeti.

Doutrelepont (6) found then in the placenta in freshly acquired syphilis. Dohi and Tanaka (7) first found *Sp. pallida* in the cerebro-spinal fluid.

Several observers, Doutrelepont and Grouven, (6) Tomaszewski, Hoffmann (8) and others found *Sp. pallida* in the border zone of intact human gummata.

The next step was to prove the presence of *Sp. pallida* in sections of tissues. This has been accomplished by means of the silver impregnation method introduced by Volpino and elaborated by Levaditi.⁽⁹⁾ The *Sp. pallida* has been demonstrated in almost every organ of the body including blood-vessels in cases of tertiary syphilis, viz. in Aortitis and cerebral arteritis, by means of Levaditi's method.

SECTION II.

EXPERIMENTAL SYPHILIS.

I. Experiments of Metschnikoff and Roux. (10)

During 1903 at the Pasteur Institute these investigators succeeded in inoculating anthropoid apes, in this case chimpanzees, with the virus of syphilis. They produced typical primary sores and characteristic secondary manifestations of the disease by further inoculation of other apes from primary sores and papules of the original animals. In other words they produced a constitutional disease in these animals, analagous to that occurring in the human species. This was an achievement of far reaching importance. They noted that the region of the eye-brow forms the best site for inoculation.

Soon afterwards it was discovered that the lower apes as well are susceptible to inoculation though to a lesser degree. Then Bertarelli⁽¹¹⁾ found that rabbits can be inoculated, the testicle being the best site.

These results opened up a field for investigation which has led to results of transcendent importance especially with regard to therapy.

II. Researches of Neisser in Java and Breslan.

Neisser⁽¹²⁾ organised an expedition to Batavia in 1905 and assisted by capable fellow-workers conducted a far-reaching and exhaustive series of

investigations.

A limitless supply of lower apes was at their disposal for experimental purposes, namely *Macacus cynomolgus*, *M. nemestrinus* and *M. Niger*. Of higher apes there were Gibbons and Orang-utans, no chimpanzees being found outside West Africa.

They commenced work in March 1905 and concluded the research in Batavia by March 1908. Returning to Breslan they then continued their investigations and finally published a quantity of most valuable results. (12)

They did a vast amount of experimental work both in the field of therapy and that of serum investigation, for purposes of diagnosis and control of treatment.

They demonstrated in a clear manner that in Syphilis there is no such thing as true immunity, and that probably no immune serum would ever be obtained to treat the disease.

Whether the discovery of the *Spirochaeta pallida* and the growing of a pure culture of it will cause a change in this standpoint, remains for the future to disclose.

The experimental research of Neisser and others as well as the discovery of the *spirochaeta pallida* have taught us much in regard to the Pathology and Diagnosis of human Syphilis.

For the practical medical man the demonstration of the *Spirochaeta pallida* is of more importance than any inoculation test. Still for scientific investigation inoculation proofs will always remain of the utmost value.

I shall name the more important results in so far as they have a bearing on the subject of human syphilis.

CHARACTERISTIC PRIMARY SORES HAVE BEEN PRODUCED BY:-

- i. a. All manifestations of human syphilis.
 - b. The blood.
 - c. Spermatic fluid.
 - d. Organs and Coryza of congenital syphilitic children.

ii. Products of syphilis in monkeys.

- a. Primary sores.
- b. Secondary papular lesions of skin and mucous membranes.
- c. Spleen, liver, bone-marrow, testicle, ovary and glands.

iii. Products of syphilis in rabbits.

INFECTIVITY OF LESIONS.

a. Primary and Secondary.

Moist papules and broad condylomata are the most highly infectious followed by fresh and still weeping primary sores.

Sclerotic lesions are infectious but, owing to the irregular distribution of spirochaetes to a lesser degree.

Fresh and dry papules on the body constitute excellent inoculation material.

Primary sores that are in process of healing give uncertain though sometimes positive results. For example Arning and C. Klein^{(12)^A} had a positive result seventeen times and only twice a negative one, using either entirely healed or almost healed primary sores as inoculation material.

These results have an important bearing on the questions of contagiousness and recurrence.

CONTAGIOUSNESS.

The remains of primary and secondary lesions especially when situated on lip or genitals demand our earnest attention. As long as any kind of infiltration is demonstrable the possibility of infection remains, for herds of spirochaetes are lying in the tissues and very near the surface.

RECURRENCE.

Recurring manifestations of Syphilis usually show themselves at sites formerly the seat of primary or secondary lesions. In latent syphilis these shut up herds may remain for a long time quiescent but, there is no doubt, they are responsible for both recurrence and to a certain extent metastasis.

Hence follows the great importance of vigorous and thorough local treatment.

These latent herds of spirochaetes are no doubt also the cause of Lencoderma and patchy loss of hair sometimes seen when no other recurring skin eruption is manifest.

Histological examination of the skin in case of latent syphilis without a trace of clinical signs whatsoever, showed changes not seen in normal skin.

Spirochaetes can therefore exist for a longer or shorter period in the skin without causing any manifest clinical appearances.

The superficial covering in cases of mixed Chancre, Malignant syphilis and Pustular syphilides, is but poor inoculation material.

Ulcerating forms of so called malignant syphilis proved particularly amenable to arsenic treatment, notably with Arsacetin, Arsenophenylglycin and Arsenobenzol, where in many cases Mercury either failed absolutely or even did harm. (13)

In malignant syphilis spirochaetes are as a rule difficult to find.

b. Tertiary Syphilis.

Generally speaking a positive inoculation is difficult.

Material aspirated from quite intact gummata or obtained from non-ulcerated scleroses, inoculated either on the eyebrow of apes or rabbit's eyes, gave various results, sometimes positive and sometimes negative.

Material from broken down gummata gave a negative result. In fact by aggregating the statistics available⁽¹⁴⁾ in certain experiments conducted on the person of fifty-eight healthy human beings, in each and every case inoculation with broken down gummata proved negative.

It does not matter whether the lesion is comparatively young or old, for Hoffmann inoculated with a positive result from a twenty-four years old case of syphilis.

Microscopic examination of tertiary lesions has proved beyond doubt that the *spirochaeta pallida* is demonstrable though only with great difficulty after a long search and many failures⁽¹⁴⁾.

Syphilis caused by tertiary material is in no wise different from the ordinary type. Consequently the peculiarity of the tertiary lesion must be regarded as due to a change in the tissues themselves, and not to an alteration in the nature and virulence of the *spirochaeta pallida*.

INFERENCE DRAWN FROM THESE RESULTS FROM THE PRACTICAL
STANDPOINT.

- i. Every individual with tertiary lesions must be regarded as a carrier of *Spirochaeta pallida* of ordinary virulence.
- II. Every tertiary process is inherently though not necessarily contagious.

Ad I.

A. An individual in the latent tertiary stage may get a recurrence of lesions that resemble those of the secondary period, being rich in Spirochaetes and equally contagious.

Such lesions are usually situated on the skin and in the mouth and consequently the danger of infection is not to be disregarded.

On the other hand there are tertiary processes apparently purely local in character, whose spirochaetes do not biologically influence the organismus.

Examples of this are:-

- i. Cases with negative Wassermann reaction.
- ii. Cases which never have lesions appearing on any other part of the body, and which are susceptible to inoculation with the production of a typical primary sore.

B. Every case of tertiary syphilis must be treated in exactly the same manner as any primary or secondary one.

Energetic mercury administration is indicated and wherever lesions are present the administration of Iodide is to be added.

Baths and sweating agents generally are advisable as there is reason to suppose that they might

possibly tend to stir up enclosed herds of spirochaetes and render them accessible to the medicament administered.

Ad II. viz. that every case of tertiary syphilis is facultatively contagious.

Primary and secondary lesions are dangerous, because they possess numerous spirochaetes and are situated on such parts, namely, genitals, lips and mouth, that offer especial facility for infection, both from their site and the liability to injury of the epidermis.

Further, secondary lesions appear sometimes of such insignificant nature that the patient's attention is either not called to them, or else he totally disregards them.

Tertiary lesions in comparison show a different state of affairs.

The intact gummata are covered with sound skin and rendered comparatively safe, whilst broken down gummata are not highly infectious at all, and in all recorded cases inoculation proved negative.

Localisation is seldom on genitals, lips and mouth.

Lesions are usually found on the extremities breast and back.

In addition, either owing to pain or the ulcerating nature of the lesion its presence is always evident and the patient is conscious of his trouble.

Quite apart from their small degree of infectiousness, such patients do not come into contact with others very intimately as a rule.

Hence the probability of contagion in case of tertiary lesions generally is relatively of a lesser degree, but we must not lose sight of the fact that they can prove infectious, and should act and give advice accordingly.

VIRULENCE OF LYMPHATIC GLANDS.

Positive results were the usual sequel. Both aspiration with a hypodermic syringe and extirpation were practiced in securing material for inoculation, and in nearly every case from comparatively recent syphilitic infections. There was only one older case (Hoffmann)(15) But it seems to me that it would have been more valuable had the experiments been conducted to a greater extent in quite long standing cases of the disease, where the syphilis was uncertain. In my opinion there is far too much importance attached to swollen glands as diagnostic values in ancient cases of syphilis.

INFECTIVITY OF THE BLOOD.

Relatively few positive results have been obtained by inoculation and the great majority of investigators failed. However, Hoffmann (16) is credited with three positive results in syphilitic infections six weeks, three months and six ^{MONTHS} ~~weeks~~ old.

Microscopic examinations of blood from veins in a healthy portion of the skin have shown the presence of spirochaetes but only isolated examples and only in a small proportion of the cases examined.

Therefore in recent cases of syphilis it is advisable to consider the possibility of blood infection, and chapped hands or cut fingers should be

protected from the chance of infection, slight as it is. The *Spirochaeta pallida* has never been demonstrated in menstrual blood but Brumpt⁽¹⁷⁾ has demonstrated Spiroch. Duttoni in it.

INFECTIVITY OF THE SPERMATIC SECRETION.

Finger⁽¹⁸⁾ has succeeded twice in getting a positive result.

Neisser failed to do so in seven experiments with spermatic fluid, but frequently succeeded when inoculating with testicles from syphilitic monkeys.

Mireur⁽¹⁹⁾ experimented on the human subject and failed in every case to get a positive result. He strongly maintains that spermatic secretion is not infective. Certainly, so far no spirochaetes have been demonstrated in it. Finger's positive results are of extreme importance. It leads us to the consideration of the possibility of so called paternal congenital infection.

I shall describe his two cases in a few words.

Case I.

Fluid obtained by massage per rectum of seminal vesicles and the prostate gland. The secretion obtained was perfectly normal, free from blood and pus corpuscles with numerous and normally active spermatozoa present.

The inoculation of an ape resulted in the production of a typical primary sore.

Finger's experiments can be considered quite genuine and there was no contact of the fluid used with any syphilitic lesion.

Case II.

Spermatic fluid obtained in a similar manner from a man suffering from a double interstitial orchitis. The infection was three years old. There were no Spermatozoa present. Inoculation on the eyebrow of an ape was followed thirty-six days later by the appearance of small pale nodules at the site of inoculation. These were not genuinely typical signs, but rightly, Finger regarded them as highly probable signs of a positive result.

This second case is interesting because there was no secretion from the testicles in the inoculation fluid, as there was in case I.

As previously mentioned, when employing testicles themselves, inoculation very frequently proves positive.

But it has not been proved that the spermatozoa are the infecting source. How are we to imagine an infection by spermatozoa?

Is there a stage of development of the *Sp. pallida* unrecognisable by the means at present at our disposal?

Is it possible that the spermatozoa merely transport the spirochaetes? But we possess no indication of such an occurrence.

It is quite thinkable to imagine an infection of the spermatic secretion through contact with papular syphilitic lesions of the prostate and urethra. However nothing sure is known about infection by spermatic fluid in human beings. Such an infection might take place by lodging in the cervix or body of the uterus.

PATERNAL INFECTION.

i.e. the direct infection of an ovulum or a fructified and developing ovulum a patre.

There are three possibilities for the mother.

- i. She becomes infected at the same time as the ovulum.
- ii. She remains perfectly healthy.

These are the cases which have been described as exceptions to the Colles-Beaumes law; exceptions because they have not become immune to post partum syphilitic infection, but are perfectly healthy individuals, just as easily susceptible to infection with syphilis as any normal individual.

An analysis of the extant literature on this point shows that opinions are divided. Several authors⁽²⁰⁾ (Matzenaner, Pernet, A. Lucas, Baisch, Rietschel) deny that such cases can exist. They enunciate the formula "no congenital syphilis without maternal infection".

Men who marry after a comparatively recent

attack of syphilis can have healthy children if the wife remains uninfected. (Jullien, Carle).⁽²¹⁾

One sure case is quite sufficient to prove the possibility of a spermatopaternal infection of the ovulum.

Such a case has never come under my observation but in the literature on the subject cases do exist where a perfectly healthy woman has borne a syphilitic child which was infected a patre. (de Keyser, Bergh, Travis Drennen, Oglivie, Sternthal, Scarenzio, Gaucher, Bory, Freck, Cuth, M. Zeissl).⁽²²⁾

iii. The mother becomes infected from the child which is rendered syphilitic a patre.

With all the clinical methods of examination usually employed we cannot prove any syphilitic infection in some women who nevertheless have a certain amount in common with ordinary syphilitic persons.

They appear healthy but remain refractory to either accidental or intentional syphilitic infection.

Such mothers can offer the breast to a syphilitic infant with impunity.

In no single case has infection of the mother resulted.

Are these women really infected or are they rendered immune by chemical protective substances that either pass from the child to the mother or are directly manufactured in the mother?

In my opinion they remain refractory because they are already infected with syphilis.

The various serological investigations show that the majority of such women give a positive Wassermann reaction.

Buschke demonstrated the *spirochaeta pallida* in lymphatic glands taken from such subjects. In this manner the majority of such so called immune cases have been proved to harbour the organism of syphilis somewhere in the system.

The next point to discuss is, how does she acquire it? Does she get it primarily from the man or by choc en retour from the child? In practice it is quite common to meet with women who deny all knowledge of infection. There has never been anything of the nature of a primary sore, yet they develop typical secondary signs of the ordinary characters.

But in this particular case we are discussing there are no secondary signs at all, and the women appear perfectly healthy.

How are we to explain this remarkable course of syphilis without a trace of secondary signs?

Doesn't it seem likely that equally remarkable concomitants of infection play their part in producing the phenomenon?

The theory of choc en retour, where the mother is infected by the child through the placenta, leads

us to imagine some venous infection perhaps not through one single large influx of masses of spirochaetes, but more probably through the penetration of a few spirochaetes on one occasion or at intervals, whose conspicuously active movements enable them to wander afield and burrow their way through the walls dividing the placenta from the mother.

Perhaps these spirochaetes would be intercepted by the glands in the pelvis.

In this manner one could quite well explain the constitutional symptoms these women show, namely, resistance to new infection and positive Wassermann, without on the other hand having to wait for such an increase of spirochaetes that they have to express their presence by means of skin eruptions and the like. This same hypothesis can be advanced in those cases where we imagine an intra-uterine infection whether from spermatic fluid or otherwise where the phenomena of menstruation favour infection.

Lastly, there is still another hypothesis to mention, namely, that it is not an actual infection of the mother, but a poisoning with syphilitic toxine through the placenta without a passage of spirochaetes.

But the relations of the serum method of diagnosis shatter this hypothesis, for the positive reaction is regarded as a sign of the presence of actual spirochaetes in the organismus which manufacture a constant supply of "Reagine", a necessary

factor in the reaction. Also long after the birth of syphilitic children the woman remains positive, which indicates that somewhere in their body spirochaetes are lurking.

There are two further facts which support the theory of paternal syphilis.

- i. Treatment of the man leads to the birth of healthy children.
- ii. A new marriage with a healthy husband also leads to healthy children, only when of course ^{SHE} has not acquired syphilis from the previous husband.

Mothers milk has proved non-infectious.

Spinal fluid has been proved infectious.

Coryza secretion is infectious.

Sputum, sweat and urine of congenital syphilitic children can be a source of contagion.

Serum of human syphilitic blood is absolutely harmless. A very large number of experiments have been made, and not a single one of them succeeded in infecting an animal.

SECTION III.

METHODS OF EXAMINATION.

This includes the procuring of material, observation in a fresh condition, the staining of slide preparations, and identification in the tissues by histological methods.

A. PROCURING OF MATERIAL.

This is of first rate importance. Mistakes and false results are very frequently due to lack of experience, skill and perseverance.

The secretion from a broken down primary sore or papule is not always the best material. This should be carefully removed by means of gauze soaked in saline solution, and then material for examination is procured by one of two methods. Either employ irritation method of Hoffmann ⁽²³⁾ or the aspiration method of Zabolotny. ⁽²⁴⁾

i. Irritation method.

Rub the cleansed lesion with a firm loop of platinum wire previously passed through a flame.

ii. Aspiration method.

Use a Klapp cup and a strong rubber ball.

Schuberg and Mulzer ⁽²⁵⁾ have produced a Klapp apparatus possessing a small hollow in which the serum collects.

The serum obtained by these methods contains the largest number of *Spirochaeta pallida*, and avoids admixture with the numerous bacteria which are always present.

If these methods fail, which sometimes occurs, scrape away some tissue from the edge of the lesion. A good ooze of serum occurs.

In such cases already treated with antiseptics calomel, iodoform, &c., the lesion must be well washed with saline solution and a gauze or mull dressing applied for twenty-four hours.

The next day one usually succeeds in finding the *spirochaeta pallida*.

I have had two cases where all these methods failed but strong suspicion was nevertheless entertained. There were no secondary signs whatsoever. I ~~exercised~~ the lesions and was able to demonstrate the presence of *spirochaeta pallida* by Levaditi's silver impregnation method.

Whenever a lesion is ~~exercised~~ it is always advisable to squeeze some serum out of the papillary zone and examine for *Spirochaeta pallida*.

Unbroken lesions should be scraped carefully with a spoon or scalpel, removing the horny layer and avoiding bleeding as much as possible.

In this way one gets suitable serum from the rete and papillary layers.

In the case of gummata and other tertiary lesions, only the examination of the periphery offers

chances of success.

From pemphigus bullae of the newly born and from pustular lesions of adults, the best serum is obtained by removing the covering and scraping the base of the lesion, as the *Spirochaeta pallida* are not numerous in the fluid of these lesions.

Lymphatic glands can be punctured with a hypodermic needle, using a syringe of about 5 ccm. capacity, possessing a long and sufficiently strong platino-iridium canule.

Puncture the convexity of the cortex and pass the needle through the greatest diameter of the gland, aspirating gradually and powerfully as the needle is withdrawn, in order to get serum from different parts of the gland, owing to the irregular distribution of the herds of spirochaetes.

In the case of internal organs, placentas, etc. sponge away the blood from a raw surface until nothing but serum is oozing. Then make your preparations from the edge of any visible lesion, or from the neighbourhood of a vein.

The examination of the blood can be best made by puncturing a cubital vein.

Noeggerath and Staehelin⁽²⁶⁾ recommend catching the blood, 1 ccm. in amount, in 10 ccm. of a 1/10 per cent acetic acid solution.

By the aid of an electrical centrifuge obtain a deposit which is spread out on slides ready for

further examination.

This is a cumbersome method and not to be recommended in practice.

The examination of a drop of blood from a pricked finger, under the darkfield illumination gives just as good results.

However examination of the blood has nothing more than theoretical interest.

B. EXAMINATION OF FRESH SERUM.

Apparatus, &c.

A good microscope with a dark ground illumination is necessary.

The ordinary 1/12 oil immersion lense is not enough. The best apochromatic apparatus is essential. It has proved a most valuable asset in the recognition of the presence of *Spirochaeta pallida*, first introduced for this purpose by Landsteiner and Mucha,⁽²⁷⁾ who employed a Reichert apparatus.

Reichert's "Spiegelkondensor" affords a very good illumination. The new apparatus, the so called "Plattenkondensor" can be applied to any microscope. An electric arc lamp or a clear ~~Auer~~ light serves as illumination. The examination can be made most satisfactorily with objective No. 5 Reich, and Compans. Ocular No. 18. The apparatus recommended by Hoffmann and the one most suitable for more exact scientific examination is the Zeiss arrangement. The Leitz system is undoubtedly a good one.

Use a Compens. ocular No. 6, though Nos. 8, 12 and 18 are good and useful. The Zeiss Paraboloid Kondensor in combination with the new Mikro-Nernst lamp is a first class apparatus. (Apochromat 2 m.m., 1,3 or 1,4 aperture).

The Nernst lamp as supplied by Carl Zeiss has the advantage of being exceedingly convenient, adaptable to both dark ground illumination as well as ordinary microscopic work. It is durable and with ordinary care will keep in order for a considerable time. I have had experience with various types of apparatus and agree that the Zeiss arrangement is the best, having one for my own private use.

After connecting the Nernst lamp to the electric current the glow wire has to be heated for a few seconds before the light appears. A small spirit lamp called the "Tinol" is very convenient for this purpose throwing, as it does, a horizontal flame.

There is an indicator included in the Nernst apparatus which shows when the current is passing. Always turn off this light before disconnecting from the main current.

A movable table attached to the microscope is a great advantage and ensures a thorough and convenient examination.

Patience and quiet are essential, combined with care and thoroughness.

Slides must be scrupulously clean. For laboratory work and clinical work where many slides and cover glasses are required, it is a good plan to follow Van Ermengen's method.

Take concentrated H_2SO_4 6 parts

Pot. bichromate 6 parts.

Aqua 100 parts.

Leave in above solution for 12 hours.

Wash in water until all traces of bichromate are removed. Thereafter preserve in absolute alcohol.

For ordinary purposes it is convenient to cleanse slides and cover glasses by means of unrectified benzene and a soft linen cloth.

METHODS OF EXAMINATION.

A. Dark ground illumination.

Take a clean slide and aided by a glass rod place a small drop of physiological saline solution (0.85%) upon it.

Mix with this a loopful of serum and apply a cover glass, which is then surrounded by wax to prevent evaporation and undue movements of the fluid to be examined.

The ordinary cover glass method is much more suitable than the hanging drop method.

Meirowsky has recommended a method of staining living spirochaeta.

A paste made of saline solution and methyl violet crystals is rubbed into a lesion and after a minute the serum is obtained and examined as above described. The *Spirochaeta pallida* is stained a bright violet colour, whilst *Spirochaeta refringens* is stained blue-violet.

For practical purposes this method is not of great value.

B. Burri's Method.

This consists in mixing fresh serum with Chinese ink and examining with 1/12 oil immersion lense in cedar oil. Suitable inks are:-

1. Pelikantusche, a preparation of Dr. Grubler, Leipzig, nine times diluted with physiological saline solution and sterilized.

2. Gunther Wagnersche Perlusche.

I prefer the latter and carry out the process in the following manner.

Prepare two strong platinum wires by twisting in such a manner so as to form flat circular plates e.g.

It is essential to have thoroughly clean slides free from fat.

Have a spirit lamp burning and a supply of aqua dest.

Then prepare your lesion and have serum flowing in sufficient quantity.

Place a drop of ink and a drop of aqua dest. on one end of a slide and mix thoroughly with the platinum coil.

Take the second platinum coil; gather some serum and proceeding rapidly mix with the ink for 10-15 seconds.

Take a cover glass immediately and spread the fluid evenly over the slide, similarly to preparing a blood film.

In the course of one or two minutes it dries, and is ready for examination under the oil immersion lense in cedar oil.

It requires some little experience to obtain the best possible result, but it is undoubtedly a useful method, and quite valuable for those who do not possess a microscope with a dark field illumination. I introduced this technique of Burri's method at Breslan and my colleagues found it quite useful. One sees the spirochaetes shining white in a field that varies from fawn to a dark brown colour. It cannot, however, compare with the dark ground illumination which enables one to see those characteristic movements of the *Spirochaeta pallida* which will be fully described later on.

C. Staining of Slide Preparations.

Make films just as for blood preparations using

plenty of serum.

After drying in the air, fix by immersing in absolute alcohol for 10 minutes or in methyl alcohol for 2 - 3 minutes.

Exercising due care one can fix over a flame, but I do not recommend it.

Best of all is the osmium vapour fixation method.

These are several quite useful staining methods.

The following methods are for practical purposes excellent.

1. METHOD OF HOFFMANN AND HALLE.⁽²⁸⁾

Fix with osmium vapour.

Well cleaned slides are laid on a vessel containing 5ccm of a 1% osmium solution + 10 drops of glacial acetic acid for 2 or 3 minutes.

The smears are then quickly made on the under surface and replaced over the osmium vapour to be acted on for 1 - 2 minutes, not any longer..

Then allow the film to dry in the air.

Next stain in ~~Giemsa~~ ^{Giemsa} solution.

Take 9 drops of ~~Giemsa~~ ^{Giemsa} solution to every 10ccm of aqua destillata.

Do not shake vigorously, merely invert the measuring cylinder once or twice. This is quite sufficient.

When examining several slides at once I have found it convenient to utilise a Petri vessel just large enough to accommodate two slides lying side by side. Place wooden matches under the ends, and if necessary add a second or third tier of matches and slides.

Place the film side undermost to avoid precipitate forming on it and obscuring it.

Always make careful notes of your slides and don't trust to memory.

After pouring in the staining solution put on a cover and leave for not less than one hour. In my experience the best average preparations are got by leaving in the stain for from 12 to 24 hours.

As the rest of the material is stained along with the spirochaetes, it is a good plan to differentiate in a 30% watery tannin solution, for about half a minute.

Wash carefully in water.

This clarifies the picture and removes any precipitation that may have occurred.

The result is good; the form of the spirochaetes is well kept and the stain is intensive.

2. A RAPID METHOD OF STAINING ACCORDING TO PREIS. (29)

Make thin smears on a slide in which under the lower power of the microscope the R.B.C^s appear isolated and intact in a colourless ground.

Grasp the slide with a suitable holder. Make a line with a glass pencil to prevent the fluid to running on the holder.

Pour on it a mixture of 20-25 drops of Giemsa solution well shaken in 10 ccm of aqua destillata.

Hold this 5 cm high above the bunsen flame of medium size until steam rises, taking care to avoid boiling away the solution.

On steam arising pour off the solution and add fresh stain.

This procedure ^{is} repeated 3-5 times until the R.B.C^s are stained an intense rose-red colour under the low power of the microscope.

This is the guide to the proper staining of the film. Wash for a short time in water. Dry with filter paper and examine under 1/12 oil immersion lense in cedar oil.

This results in an intensive red staining of the Spirochaeta Pallida.

Giemsa has modified this method slightly in so far as he takes 1 drop of Giemsa solution to 1 ccm of water, and after each heating allows the stain to act for $\frac{1}{2}$ minute before pouring off.

3. SCHERESCHEWSKY'S⁽³⁰⁾ Method

He takes 13-15 drops of the original Giemsa solution and boils this in 10 ccm of a $\frac{1}{2}\%$ of glycerin solution in aqua destillata in a perfectly clean test tube.

There must not be any precipitation.

The hot solution is poured on to the preparation and left for 2-3 minutes, conveniently supported by two glass rods.

If the film is not stained sufficiently red after washing in water, repeat the process. A very strong staining of the *Spirochaeta pallida* results.

4. LÖFFLERSCHE GEISSELFARBUNG.

This is excellent to represent the more exact structure of the *Spirochaeta pallida*.

Take thin smears of serum fixed either in osmium vapour or alcohol.

Pour on a solution called "Löfflersche Beize", which consists of:-

10_{ccm} of a 20% Tannin solution.

5_{ccm} of a cold-saturated Ferro-sulphate solution.

1_{ccm} of a saturated alcoholic Fuchsin solution.

This is heated until steam rises and exercising great care this is repeated three times.

Wash with aqua destillata.

Then stain with Ziehlschen Carbol. fuchsin cautiously warming meanwhile. Wash in water, Dry in the air.

Apply a cover glass with Canada balsam. This gives intense staining of *Spirochaeta pallida*, whilst the end flagellae are more faintly stained.

D. Representation in Tissues.

This has been successfully accomplished by means of silver impregnation.

The disadvantage is that the finest elastic fibres are stained black in a similar manner to the *Spirochaetes*, and very occasionally it may be difficult to differentiate. Generally speaking however it is possible to distinguish between them.

Volpino⁽³¹⁾ was the discoverer of the method originally worked out with E. Bertarelli, and now only of historical interest. This method involved the staining of paraffin sections.

It was Levaditi⁽³²⁾ who modified the process by substituting the treatment of pieces of tissue, following the experience of Ramon-y-Cajal, and made the process generally useful and practicable.

I shall only describe the new Levaditi method which I have personally proved to be of value.

1. Fix the piece of tissue not more than $\frac{1}{4}$ inch thick in 10% Formalin solution for 24 hours.
- A longer period in Formalin does not matter.
2. Lay the pieces in 90-95% alcohol 24 hours.
3. Place in aqua destillata frequently changed until the pieces sink to the bottom.

4. Impregnation in Silver nitrate and Pyridin.
This mixture must always be freshly prepared and consists of:-

90_{ccm} of a 1-1.5% watery solution of Silver Nitrate.

10_{ccm} of purest Pyridin.

It remains for 2-3 hours at the room temperature and a further 3-5 hours in the paraffin oven at 45^oC. never more than 50^oC.

Employ dark glass bottles with glass stopper and from No. 4 to No. 6 work in as much dark as possible.

5. The Silver nitrate solution is poured off and after a short washing in aqua destillata or better still without it, the following reducing mixture is added:-

90_{ccm} of a 4% Pyrogallol solution is mixed with 10_{ccm} pure acetone.

To 85_{ccm} of this mixture

15_{ccm} Pyridin is added.

The pieces remain in this mixture 24 hours.

If cloudiness appears, change the solution.

6. Wash in aqua destillata.

7. Hardening in alcohol in the following manner.

Place in 70% alcohol for 15 minutes.

" " 95% " " 20 "

" "absolute " No 1 " 15 "

" " " " No 2 " 15 "

8. Place in Xylol till clear.
9. Place in paraffin oven at 55°C for 3 hours, having three vessels of pure paraffin whose melting point is $52-53^{\circ}\text{C}$, leaving pieces 1 hour in each.
10. Imbed in paraffin and cut sections as thin possible, e.g. 2μ afterwards fixing sections on slides in oven at 37°C for 2-3 hours.
11. Remove paraffin with Xylol.
12. Pass through absolute alcohol to remove Xylol and mount in Canada balsam.

The tissue tone is a clear yellow and the *Spirochaeta pallida* shows up perfectly black, most delicately impregnated.

E. Morphology and general description of *Spirochaeta pallida* as it appears in fresh serum and in stained specimens.

The *Spirochaeta pallida* has a long delicate and thread like form with extremities running into points. It possesses numerous and regular undulations characterised by their sharpness and rather close juxtaposition, described by Schandinn as a curve of a corkscrew-like nature.

It is usually $\frac{1}{4}\mu$ in thickness, and in consequence difficult to recognise in the fresh state, especially as it exhibits but small refractive powers to light.

Its length varies considerably, the number of undulations fluctuating from but a few to as many as 26 or even more in rare cases. On the average the

number is from 8 to 12. Accordingly the length varies considerably and from 10-15 is about the average number of undulations.

This great length in proportion to the thickness is one of the most important characteristics of the *Spirochaeta pallida*.

Viewed in the dark field illumination in a condition of rest it tends to form a straight line in general direction always retaining its undulations. In fully formed individuals the curves are deeper in the middle and diminish somewhat towards either end.

Exact measurements in specimens fixed by the Osmic acid method and stained according to Giemsa show that the length of the undulations averages 1.0-1.2 , whilst the depth is 1.0-1.5 . (Hoffmann, Hartmann and Muhlens)(33)

It is this relationship between the length and depth of the individual undulations, which, in association with the extreme fineness of the thread, affords a characteristic picture not presented by the other spirochaetae of a similar form and regularity.

In fresh unstained specimens the *Spirochaeta pallida* exhibits a homogenous nature of its thread. In the dark field illumination it appears luminously white. Differences between the envelope and inner substance are not recognisable.

Nevertheless in the course of the thread some-

what more strongly refractive points can be made out, if one employs the Zeiss system. These perhaps correspond to the nuclei that take on the stain more deeply in some specimens one examines.

In a fresh condition the *Spirochaeta pallida* has very lively movements. It can rotate on its long axis, and glides to and fro with a screw-like motion. It makes bending movements from side to side and can change the length and depth of its individual curves.

In a state of rest it has a corkscrew-like appearance. There is a suggestion of stiffness about the movement which many observers have noted. But *Spirochaeta pallida* belongs to the group of so called flexible micro-organisms, and this appearance of comparative rigidity is more a great degree of elasticity possessed by the thread-like body.

The movements are most lively shortly after leaving the living body. The *Spirochaetae* travel about from place to place until they come to rest, frequently with one end in contact with a Red blood corpuscle, still continuing to carry out rotatory and bending movements.

The side motion is at first the most frequent and the *Spirochaeta* forms itself into a wreath, unrolls itself again to repeat the procedure.

Another movement suggests a worm wriggling in a jerky manner.

Gradually the motion ceases after a period of from 24 to 48 hours and often sooner.

It maintains its form for several weeks and consequently possesses great resisting powers. The smaller *Spirochaetae* appear to remain active for a longer period than the larger varieties, and in the case of congenital syphilitic children this vigour is especially well marked.

I have watched *Spirochaeta pallida* for hours at a time under the dark ground illumination.

The very vigorous ones suggest a boring power when in the course of an excursion they impinge on some obstacle. It is quite possible that their "end threads" play an important role in facilitating the penetration of tissues and cell protoplasm as well as vessel walls.

The nature of the finer structure of *Spirochaeta pallida* is difficult to determine, on account of the extreme smallness of the organism.

Opinions vary considerably.

There is practically unanimity that the transverse section is circular in form, and that the body is cylindrical and not of a tape form.

Certain *spirochaetae* possess a tape form and an undulating membrane e.g. *spirochaeta buccalis* and *spirochaeta refringens* (Schandinn), *spirochaeta vincenti* and *spirochaeta balanitidis* (Hoffmann - Prowazek).

As far as we know at present the spirochaeta pallida does not possess an undulating membrane, and neither has it got lateral flagellae.

✓Prowazek and Hartmann⁽³⁴⁾ have studied the structure of the larger spirochaetae. They called the outer envelope the "Periplast" which in the larger varieties is somewhat flabby, supposedly largely consisting of lipid, and under certain conditions showing lateral flagellae resembling fibrils.

The Plasma enclosed by the Periplast contains chromidien, i.e. chromatin in the form of the finest granules, arranged in rows along the axis of the spirochaeta, and in the largest size of spirochaetae looks like a solid rod like nucleus.

Schellack and J. Gross⁽³⁵⁾ dispute this.

However in the case of the thin spirochaeta pallida none of these appearances can be made out.

Besides the normal type of spirochaeta pallida one meets with some which differ from it in form and construction.

Herxheimer⁽³⁶⁾ was the first to describe nodular and stainable swellings of the body which he designated nuclei and centrosomes, and at the same time described the presence of peculiar Endkörperchen. It is quite true that one does at times meet with nodular swellings which show themselves in the dark field as points of a greater refractive power.

Herxheimer admits that sometimes this consists of granules grouped around the Spirochaete. Nevertheless it seems possible that there does really exist some more thickly arranged accumulations of the usually diffusely spread chromatin substances.

Some observers have designated these nodules as spores without any evidence to support their contention.

Noguchi⁽³⁷⁾ for example describes spore-like nodules seen in pure cultures, stainable by Giemsa and visible in the dark field. Kryzstalowiez and Sie^dlecki⁽³⁸⁾ have described clear points surrounded by strongly stained granules in Giemsa preparations. They describe this appearance as analagoue to the well known clear areas of the nucleus body, (Achromatin surrounded by chromatin granules).

They also described certain Endkörperchen. But these appearances can quite well be artificial productions caused by the heaping up or folding up or curling up of the endthreads of the Spirochaete.

These are seen not only in Giemsa and silver preparations, but also in the dark field in preparations a few days old.

The extraordinary forms described such as the absolutely straight or only partially coiled examples are seldom seen in well fixed Osmic acid preparations.

But Fouquet⁽³⁹⁾ and others have noted that partly straight forms, frequently with the central portion

straight, and ordinary curves towards the ends, are more frequently met with in the late period of syphilis.

The granular forms are seen mainly in silver preparations. They are almost surely degenerative forms and are frequently seen in the organs of a macerated foetus, intracellular and very probably undergoing phagocytosis.

Forms possessing but a very few coils have been found by Wechsellmann and Löwenthal⁽⁴⁰⁾ in dry skin papules, especially in those that are disappearing spontaneously, or under the influence of mercury.

Noguchi finds them often in his cultures.

The extraordinary long forms might be merely the linking together of two individuals. It might possibly be a real connection of two dividing spirochaetes, still joined by a thread.

Lastly, 24-48 hours after Ehrlich's Salvarsan the spirochaetes appear plumper and swollen. They soon lose their lively movements. This phenomenon I have frequently observed.

When Salvarsan was first introduced into the Breslau Klinik, one of my duties consisted in hourly examination of the serum of patients, continuing for two and sometimes three days, lengthening the period between examinations to 2, 4 and 6 hours.

Sometimes after 4 hours the active movements diminished^{and} swollen degenerated forms were to be seen.
^

In some cases no spirochaetes at all were demonstrable, where previously they were in hordes, or if present they were no longer living. In other cases, after 24 or 48 hours living spirochaetes could be found. It was usually the freshest case of disease that lost the spirochaetes the soonest.

STAINED SPIROCHAETA PALLIDA.

Employing the ordinary staining reagents for bacteria the spirochaeta pallida is either unstainable or else takes on stain very badly.

Giemsa's method is the best.

It is stainable with ~~Au~~ilinwater-gentian-violet.

Carbol fuchsin, hot concentrated gentian violet, and to a certain degree with Löffler's methylene blue. Carbol-methylene blue and some other staining reagents. However such staining is uncertain, feeble and not of practical importance.

The Spirochaeta pallida is gram negative. In Giemsa solution it takes on a distinctly reddish tone, and does not stain so intensely as the other coarser types of spirochaetes which are mostly tinged with a bluish red tone.

This reddish tone can be regarded as a further characteristic of the spirochaeta pallida.

SECTION IV.

BIOLOGY.

A. DIVISION AND DEVELOPMENT OF SPIROCHAETA PALLIDA.

It is a disputed point as to whether it multiplies by longitudinal or horizontal division. Numerous distinguished observers hold either the one or the other view.

McDonagh⁽⁴¹⁾ has recently published some interesting papers regarding this question describing a sexual and asexual cycle of reproduction of the organism. So far his results have not been sufficiently substantiated, but there may be some truth in his elucidation of the problem.

Protozoa divide characteristically longitudinally whilst bacteris divide transversely.

One sees Spirochaeta pallida with a thin connecting thread, and occasionally specimens having either a Y or a V shape.

Schandinn⁽⁴²⁾ held the theory of longitudinal division.

Gross⁽⁴³⁾ explains the V and Y shaped forms as being Spirochaetes dividing transversely, but ^{by} chance the parts are either intimately approximated or stuck together, creating the appearance as if they were dividing in their length.

It would be rather remarkable for a horizontal dividing organism to do so by means of an attenuated thread, contrary to the usual occurrence.

Schandinn⁽⁴⁴⁾ first of all, and later on Siebert and V. Prowazek⁽⁴⁵⁾ described the division of one pole of a *Spirochaeta pallida* which advanced in the few seconds whilst under observation.

The reason why one sees the division so seldom is explained by the extraordinary speed with which the phenomenon occurs.

A further problem which still remains undecided is the question as to whether there are other developmental forms or not, in particular a resting stage.

V. Prowazek has described certain rolled up and ball shaped forms as part of the cycle of development.

Hoffmann and others have clearly demonstrated the presence of these forms which sometimes show transitional stages, partly rolled and partly sinuous, and in the blood of congenital syphilitics the presence of examples which actually roll and unroll.

Von Kryzstalowicz and Siedlecki⁽⁴⁶⁾ report a sexual reproduction of *Spirochaeta pallida*.

They describe micro and macro-gametes, &c.

B. CULTURE OF SPIROCHAETA PALLIDA.

Parodi, Neisser, Hoffmann, Uhlenhuth, Mulzer⁽⁴⁷⁾ and others have shown that the testicles of monkeys and rabbits form a suitable medium for growing *Spirochaeta pallida* in the living body, without the contaminating presence of other micro-organisms.

They thus produced a pure culture in the living tissue, and from it sub-cultures were transferred to as many as 30 testicles in succession.

These results form a splendid basis for striving after the desired goal, namely a pure culture of *Spirochaeta pallida* on an artificial medium.

In 1906 P. Muhlens⁽⁴⁸⁾ succeeded in growing a pure culture of *Spirochaeta dentium*.

Hoffmann and Beer⁽⁴⁹⁾ showed that in airtight cover glass preparations *Spirochaeta pallida* remained lively and actively motile for several days. From this they deduced that it must certainly be an anaerobic parasite.

I shall not enter into a full description of the numerous attempts made to secure a pure culture of *Spirochaeta pallida*, but shall mention some of the more important experiments.

C. Levaditi and J. McIntosh⁽⁵⁰⁾ cultivated the *Spirochaeta pallida* in small collodium sacks, placed in the peritoneal cavity of an animal, in a similar

manner to that in which Levadite had previously cultivated *Spirochaeta galli*, Duttoni and refringens. All attempts to inoculate monkeys and rabbits proved negative.

Consequently Levaditi thought that he had cultivated an avirulent variety of pallida.

In 1909 Schereschewski⁽⁵¹⁾ reported that he had grown *Spirochaeta pallida* in horse-serum but not a pure culture, whilst animal inoculation proved negative.

Next, Mühlens⁽⁵²⁾ succeeded in isolating and cultivating a *Spirochaete* which could not be morphologically differentiated from *Spirochaeta pallida*.

He used horse-serum agar, in which colonies of a fine and delicate nature grew under strongly anaerobic conditions. Within nine months 32 generations were reproduced. Again all animal inoculations failed.

Then W. Hoffmann succeeded in the same experiment using human material, viz. infected lymph glands.

In 1910 Bruckner and Galasesco⁽⁵³⁾ inoculated the testicles of rabbits with impure cultures and obtained typical syphilitic orchitis.

In 1911 Sowade⁽⁵⁴⁾ caused a generalised syphilis with skin eruption by an intra-cardial injection of impure culture into rabbits.

This fact disproved the statements of E. Hoffmann and Mühlens that the *Spirochaeta pallida* probably lost its virulence during artificial cultivation.

Finally. Noguchi⁽⁵⁵⁾ employing rabbits testicle as inoculating material grew a *Spirochaete* corresponding in all particulars to *Spirochaeta pallida*.

After countless experiments he produced a medium consisting of watery serum and fresh pieces of tissue, rendered completely free from acid and covered with a layer of paraffin oil.

In this medium the first pure cultures were produced although with great difficulty, and after many failures under the strongest anaerobic conditions.

Noguchi used ten different strains of *pallida* which were passed into rabbits through many generations.

Noguchi's culture medium.

He took tubes 20 centimetres high and 1.5 centimetres wide. To these he added 16 cubic centimetres of serum water (sheep, horse, rabbit) which consisted of 1 part serum to 3 parts distilled water.

After completion of the usual fractional sterilization at 100°C for three days, (fifteen minutes each day), a small piece of freshly removed sterile tissue is placed in each tube. Pieces of kidney, testicle or heart muscle are the most suitable. Liver is not suitable.

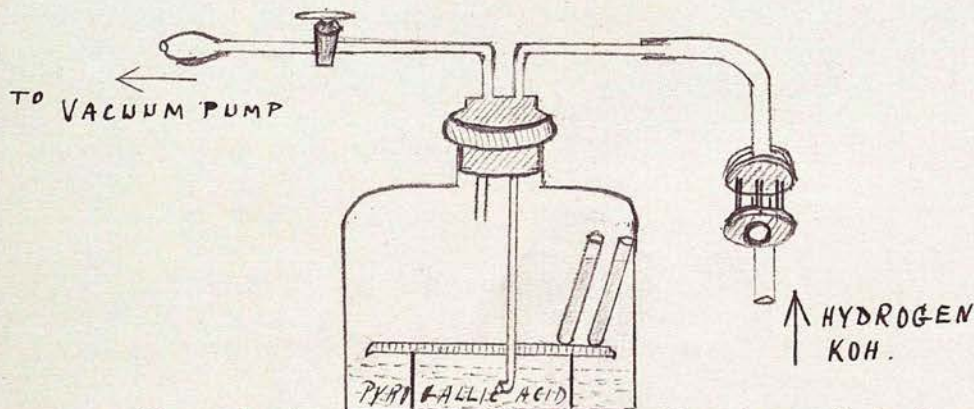
Then the tubes are incubated at 37°C for 2 days and examined for sterility.

To each tube a layer of sterile paraffin oil is now added in order to shield the medium from all contact with the air and to prevent evaporation.

Strict anaerobic conditions are very important in obtaining the first generation of *Spirochaeta pallida*.

He employs a combination of hydrogen gas, vacuum, and pyrogalllic acid in an anaerobic apparatus.

A complete anaerobic condition is maintained.



Pass hydrogen gas through the inoculated culture medium for 5 minutes with a long sterile capillary pipette before placing in the anaerobic jar.

- i. Pass hydrogen gas through the jar for about ten minutes. (When the air is driven off the jar is sealed at both ends.)
- ii. Vacuum pump for 30 minutes to exhaust the air

When exhaustion has reached its maximum a concentrated solution of KOH is allowed to flow in, (after first passing hydrogen to get rid of oxygen.)

The KOH mixes with the pyrogalllic acid, and if any oxygen is present it will turn brownish or brown, otherwise it remains clear.

Before putting the jar in the thermostat exhaust the jar once more, because this collapses the rubber tube at one end and a leak in the jar can be easily detected by the disappearance of the collapse (negative pressure) of this end.

To obtain the first generation of the treponema pallidum in virulent form the following conditions are essential.

1. The presence of suitable fresh sterile tissue in serum water.
2. Strict anaerobiosis.
3. A slightly alkaline reaction as furnished by the serum and tissue.
4. A temperature of about 35° to 37°C .

The presence of agar or gelatine seems to interfere with the successful growth of the first generation. On the other hand when once adapted to the artificial serum water tissue medium the pallidum grows well under less strictly anaerobic conditions.

All pure pallidum strains are being cultivated in a tissue containing medium.

The first strain was obtained in October 1910 and except in one instance was contaminated with the bacteria.

The pallidum was isolated by permitting it to grow through a Berkefield filter, passing through after the 5th day.

Later on it was discovered that certain strains of pallida would grow together with the bacteria

along the stab canal in a serum agar tissue medium. The bacteria did not grow out into the surrounding medium, whereas the pallida gradually grew out. This was indicated by a light, almost transparent, zone of haziness, and in this way the spirochaeta pallida was obtained in a pure state.

From this hazy colony Noguchi was able to procure pure cultures from four different impure strains.

The purified pallidum grows well in a serum agar tissue but even better in a serum water tissue medium.

The growth does not extend very far from the bottom where the tissue lies.

Noguchi was unable to cultivate the pallida in any medium without the addition of tissue.

The strains of Hoffmann and Mühlens produced a peculiar penetrating odour in serum containing media.

Noguchi's strains were odourless.

CHARACTERISTICS OF CULTIVATED TREPONEMA PALLIDUM.

In serum water they commence to multiply after 48 hours and continue to grow slowly for at least 4 or 5 weeks, probably longer.

Typical lengths and curves are seen in a 10 to 12 day culture.

The specimens grown on a solid medium are difficult to distinguish from specimens just taken from human or animal lesions.

PATHOGENICITY.

Typical lesions in testicle of rabbit were produced by Noguchi.

Tomasczweski and Sowade^(55a) succeeded in producing a generalised syphilis by injection of impure culture of *Spirochaeta pallida* into the blood stream through the ear vein of a buck rabbit. After twenty-three days an eroded papule appeared on the penis containing *Spirochaeta pallida*.

Noguchi and Hoffmann alone have reported positive results with pure cultures, and they only produced a local disease of the testicle.

Sowade^{is} at present attempting to produce generalised syphilis by the injection of a pure culture into the blood stream.

Noguchi^(55b) lays down the following conditions to be fulfilled in order to identify a cultivated spirochaete with *Spirochaeta pallida*.

1. Morphological identity.
2. No putrid odour.
3. The presence of fresh tissue is essential
4. The extract emulsion must bind complement with immune serum; (that from a rabbit is preferable) which is produced through repeated injections of the *Sp. pallida* (from syphilitic orchitis of rabbits).

SECTION V.

A. DISTRIBUTION OF THE SPIROCHAETA PALLIDA IN
THE ORGANISMUS.

In the border zone and immediate surroundings of a lesion the organism is found in greatest abundance. Lesions that have existed for a considerable time, especially severe ones, have either very few spirochaetes demonstrable or none at all.

They are mostly distributed in the walls and lumina of the lymphatic system, in the connective tissue and around the veins and capillaries, and in their walls.

They are found in great numbers in the inter-spinous spaces of the rete Malpighi, also lying in the inter-epithelial spaces and deeper layers.

They are also met with in sweat and sebaceous glands and hair follicles.

In the connective tissue they are found running along the collagenous bundles.

Occasionally in the walls of the lymph and blood vessels they form a thick network.

With relation to the cells they are usually found extra-cellular, but have been demonstrated in the interior of various kinds of cells.

They are found inside the parenchymatous cells of liver, kidney and supra-renal body, as well as sweat gland cells in congenital syphilitic children.

It is debatable as to whether it is an evidence of phagocytic action or a piercing of the cells by the pallida.

Apparently phagocytosis plays an important part in the destruction of Spirochaetes.

Levaditi⁽⁵⁶⁾ Found macrophages in the lung which contained partly disintegrated spirochaetes, whilst Gierke⁽⁵⁷⁾ found in the same organ polynuclear leucocytes filled, more or less, with spirochaetes, heaped up and in process of destruction.

Ehrmann⁽⁵⁹⁾ found spirochaetes in leucocytes and lymphocytes, in fibroblasts and endothelium of lymphatic glands, in all stages of disintegration.

But outside the cells in the connective tissue and vessel walls similar disintegration is observed, probably due to the action of anti-bodies circulating in the tissue serum.

The blood is not a favourite medium for the spirochaete which prefers anaerobic conditions.

The most favourable site is the subepithelial lymph network where they get the best protection against phagocytosis.

In this situation they rapidly increase and migrate along the lymph channels to the glands of the region. But almost as quickly they wander into the connective tissue bundles, capillaries and veins, eventually into the bloodstream, by which means they are further distributed.

The reaction of the organismus to the presence of the spirochaetes is delayed. This explains the fact of the long primary period of incubation, and the fact that one sometimes finds swarms of spirochaetes in tissues apparently quite unaltered.

B. DIFFERENTIAL DIAGNOSIS FROM OTHER SPIROCHAETES.

On the normal skin spirochaetes do not find a habitat.

On mucous membranes, however, they are quite common parasites, particularly in the mouth, and not infrequently in normal genital secretions, and in the bowel.

Spirochaetes are greatly increased in numbers in a series of diseases characterised by foul and dirty discharges, ulcerating gangrenous or fungating growths.

Besides moist papules and papillomata, one can name Balanitis erosiva et circinata, mercurial stomatitis, Angina vincenti, gangrenous ulceration and gangrene of the lungs, ulcerating carcinomata, ulcus cruris, ulcus tropicum, pemphigus vegetans, certain fevers in which a spirochaete is the etiological factor, and lastly, one we must not forget, the spirochaete pallidula, the operating cause of Framboesia tropica.

I shall describe ten varieties of spirochaetes which are to be considered from the point of view of differential diagnosis.

1. Spirocheata buccalis. (Cohn)
2. " dentium.
3. " refringens. (Schandinck and Hoffmann)
4. " balanitidis. (Hoffmann and Prowazek)
5. " Vincenti.
6. " gangraenae nosocomialis. (Hoffmann)
7. " carcinoma. (Hoffmann - Mulzer)
8. " (blood) (recurrens)
(Duttoni.)
9. " pallidula. (Castellani)
10. " in ulcus tropicum.

1. SPIROCHAETA BUCCALIS.

Length 10-20 μ Thickness $\frac{1}{2}$ -- $\frac{2}{3}$ μ . Possesses 3 - 10 flat and irregular curves. Strongly refractive, with vigorous movements of an eel or snake like character.

Compared with spirochaeta pallida.

Its ends are more blunt.

It is larger, thicker and more refractive to light.

It advances more rapidly from place to place, and its eel-like movements are quite different to those of pallida.

It stains much more easily and intensely.

Easily differentiated from Spirochaeta pallida.

2. SPIROCHAETA DENTIUM.

Length 4 - 12 μ and longer. Thickness $\frac{1}{4}$ - $\frac{1}{3}$ μ
Feebly refractive.

Resembles pallida in number of curves, form and movements.

Stains with difficulty but not so badly as pallida, takes on a reddish tone with Giemsa.

Compared with Spirochaeta pallida.

The chief difference is that the curves are not so deep as those of pallida, and it possesses a greater thickness of its thread in proportion to the excursion of a curve, whilst the fineness of the thread and its length in proportion to the great depth of the curve characterise the Spirochaeta pallida.

<u>c.f. Sp. dentium.</u>	<u>Sp. pallida.</u>
Length 4-12 μ seldom more	10-20 μ
Thickness up to $\frac{2}{3}$ μ with Löffler's stain	$\frac{1}{4}$ μ
Length of curve 1-2 μ	1.2 μ
Depth of curve $\frac{1}{3}$ - $\frac{2}{3}$ μ maximum	1.0-1.5 μ
(Relation of length 1.0 (to depth on average. 0.5	1.0 <hr/> 1.0 - 1.5
Corners of curve almost angular	rounded.
(Hoffmann, Muhlens and Hartmann) ⁽⁶⁰⁾	

3. SPIROCHAETA REFRINGENS.

Not seldom found in normal genital secretion. Especially abundant in cases of weeping papules and papillomata. They pierce the epidermis but rarely penetrate deeper.

Greatly resembles *Spirochaeta buccalis*, considered by some identical with it.

Contrasted with *Spirochaeta pallida*.

Refringens is larger, thicker and exhibits livelier movements of an eel-like nature.

Much more easily stained by Giemsa taking on a bluish tone.

The body is of a band like form and the ends are more blunted.

Finer forms of refringens are met with but are quite capable of differentiation.

4. SPIROCHAETA BALANITIDIS.

Long individuals. Thickness $\frac{1}{2}$ - $\frac{3}{4}$ μ . Band like form possessing from 6 - 10 curves.

Constantly found in cases of Bal. erosiva et cirxinata.

Greatly resembles refringens but has more frequently long end threads.

Contrasted with *Spirochaeta pallida*.

The large variety is easily differentiated, c.f. refringens.

The width of the organism is very variable, and as well as the easily differentiated large variety there are sometimes finer examples met with which perhaps correspond to what Levaditi described as *Spirochaeta gracilis*.

These are just as difficult to differentiate from *Spirochaeta pallida* as *Spirochaeta dentium*.

5. SPIROCHAETA VINCENTI.

Large and with a band like form possessing markedly broad curves. In cases of angina vincenti they are found along with the bacillus fusiformis.

Contrasted with Spirochaeta pallida.

In size they resemble the Spirochaeta buccalis but they have fewer and wider curves.

It stains much more easily than pallida and is without difficulty differentiated from it.

6. SPIROCHAETA GANGRAENAE NOSCOMIALIS.

Form is very irregular of varying length and thickness.

Contrasted with Spirochaeta pallida.

It is large, irregular, easily stained and the curves are broader, flatter and coarser than those of Spirochaeta pallida.

It resembles more the Spirochaeta vincenti.

7. CARCINOMA SPIROCHAETA.

Called also the pseudo-pallida, and found on ulcerating carcinomata. At first the differentiation from pallida seemed almost impossible, but Schandinn, Hoffmann, Mülzer and others established fundamental differences, despite the great resemblance.

Contrasted with Spirochaeta pallida.

It is thicker, somewhat coarser, less

regular curves which are flatter and less numerous. The ends are more blunted. In fresh specimens its movements do not correspond with those of pallida and it is more refractile. It stains more intensely than pallida, taking on a bluish tinge.

It stains readily with carbol-fuchsin and still more easily with carbol-gentian-violet.

It also stains readily with Borax methylene blue.

8. BLOOD SPIROCHAETES.

As far as the human subject is concerned the only ones to mention are Spirochaeta recurrentis and Sp. Duttoni and Novyi.

Contrasted with pallida:

They are larger, thicker and more easily stained, and do not come seriously into the question of differential diagnosis

9. SPIROCHAETA PALLIDULA.

The organism of *Frambæsia tropica* offers the greatest difficulty of all in differential diagnosis from Spirochaeta pallida.

Castellani and Schüffner⁽⁶¹⁾ consider a differentiation well nigh impossible.

This is very regrettable for those resident in tropical countries, but hardly affects us in Great Britain.

10. SPIROCHAETA IN ULCUS TROPICUM.

A large Spirochaeta with flat curves varying in number. Alongside this is found a smaller more compact type with but one curve resembling the balanitis spirochaete but somewhat thinner.

Taking a general survey of Spirochaetea it might seem almost impossible to differentiate between them microscopically.

It is, in fact, very difficult to classify them aright, but despite all, the practiced and skilled observer will almost always form a correct opinion as to whether the Spirochaete in question is a Spirochaeta pallida or not.

THE ORGANISMAL CAUSE OF SYPHILIS.

Since its discovery the Spirochaeta pallida has been rightly regarded as the causal organism of Syphilis.

The conditions formulated by Koch to be fulfilled before the identity of an organism can be securely established, have been complied with.

Noguchi has grown a pure culture of the organism, and the disease has been reproduced in animals by inoculation with this culture.

There is now sufficient substantiation of the claims of Noguchi, and the problem can be regarded as solved.

PART III.

DIAGNOSIS.

In the vast majority of cases a patient comes for advice showing manifest clinical signs and symptoms which, in conjunction with the history elicited, render a diagnosis of syphilis relatively easy. But now and then one meets with a case which proves baffling. There may be no history to guide, whilst the clinical signs and symptoms are either so indeterminate and unusual, or so scanty, perhaps only an erosion, that, even although suspicion is entertained it is either very difficult or well nigh impossible to decide whether it is a case of syphilis or not.

Of course, in such a case we can wait and see, what further developments take place, but by waiting for further signs we may be losing most valuable time, and actually fail to apply our treatment at that time when the disease is most amenable to treatment. Every day may be of untold value. It is in such cases that microscopic examination is demanded, and very often by demonstrating the spirochaeta pallida we have gained weeks, and can commence treatment with a reasonable hope of stamping out the disease in a much shorter time and with greater ease than if we had waited for confirmatory clinical evidence.

Neisser prefers a Giemsa stained preparation to any other means. Personally I consider that the dark ground illumination is the surest and best means of identification, provided the observer is skilled and experienced.

If the darkfield examination proves negative, I try Burri's method, and at the same time stain a few slides according to Giemsa.

Then if all these methods fail a negative opinion has a certain amount of authority.

As before mentioned I have had two cases where all these methods failed, yet I was able to demonstrate the presence of *Spirochaeta pallida* by treating an excised piece of tissue according to the silver impregnation method of Levadite.

In those cases in which there are no signs beyond the presence of swollen lymphatic glands, a puncture of the glands followed by examination of the fluid obtained, sometimes reveals the *Spirochaeta pallida*.

In every suspicious case take a sample of blood and subject it to the test of the Wassermann reaction.

THE WASSERMANN REACTION.

I do not intend to go into the history of this reaction beyond mentioning a few of the main features leading up to its establishment as one of the most important factors in our modern views of diagnosis and treatment of Syphilis.

Spirochaetes have been found in the blood, but this is a rare and inconstant sign of no value for diagnosis.

A change in the number of blood corpuscles, of the Haemoglobin index, and the amount of iron present has been looked for without disclosing anything of value for diagnosis.

The investigation as to an alleged increase in the albumen contents of the blood and the estimation of the freezing point have likewise failed.

The works of Detre and Seller⁽⁶²⁾ concerning the agglutination ability of both normal and syphilitic blood, as well as those of Nagelschmidt⁽⁶³⁾ concerning agglutination, haemolysis and precipitation have not resulted in anything of practical importance.

It was the introduction of the process of fixation of complement reaction for the diagnosis of syphilis by Wassermann, Neisser and Brück⁽⁶⁴⁾ that gave us a useful and practical means of recognising syphilis through the blood.

The historical development of this reaction reaches back to the work of Paul Ehrlich the founder of the whole question of immunity.

RESEARCHES OF BORDET AND GENGON.

In order to refute Ehrlich who maintained the plurality of complements, and to bring proof of the uniformity of these bodies, Bordet and Gengon⁽⁶⁵⁾ in

1901 made the attempt to combine a suitable complement in a so called haemolytic system, with bacteria loaded with their bacteriolitic amboceptor. These experiments had a positive result. For example if they loaded cholera vibrios with their specific amboceptor, then these sensitized vibrios were able to link to themselves guinea pig serum out of the haemolytic system; (Guinea pig complement, — rabbit - sheep's blood immune serum— sheep's blood) and through the combination prevent haemolysis.

Bordet and Gengon recognised the specific nature of this proceeding and demonstrated the diagnostic value of this so called fixation of complement reaction for the recognition of bacteria on the one hand and amboceptors on the other hand.

Later on Gengon⁽⁶⁶⁾ showed that antibodies appeared not only in the case of pure bacteria but also at the immunisation against dissolved albuminous substances (blood serum, casein &c) and that antibodies of the nature of amboceptors appear which can be demonstrated by the fixation of complement.

These experiments, however, achieved no practical results.

These came about first of all when Max Neisser and Sachs⁽⁶⁷⁾ in the year 1905 recommended the fixation of complement reaction for the differentiation of albuminous bodies in the sphere of medical jurisprudence.

Soon after, at the end of 1905, Wassermann and Brück⁽⁶⁸⁾ were able to show that the fixation of complement is not dependent on any preceding precipitation, a point of view in which Moreschi⁽⁶⁹⁾ concurred later on in his own account. They showed that the fixation of complement occurred not only with morphologically whole bacteria, but also with dissolved substances from the bodies of bacteria (bacteria extracts).

Through this the possibility was given to make use of this reaction for clinical diagnosis in two directions.

- i. The attempt could be made with bacteria extract as antigen to demonstrate the specific amboceptor belonging to it, in the serum of a sick individual, and in this way establish an indirect specific diagnosis.
- ii. The possibility of a direct specific diagnosis was given, namely, with the help of specific amboceptors (of artificially immune sera) to discover the corresponding antigen in the blood, as the dissolved substances of the microorganism concerned.

In this manner Wassermann and Brück made use of the fixation of complement with good results in Typhoid and epidemic menigitis; (also for measuring the value of menigococci-antisera). Lately the number of diseases has been increased in which this reaction finds application, - swine fever, cholera and gonorrhoea.

In the next year, in 1906, Wassermann and Brück⁽⁷⁰⁾ used the reaction for the first time to prove the presence of antigen in human and animal organ extracts.

They showed, by the aid of specific immune sera of tubercle bacilli, the presence of dissolved T.B. substances (tuberculin) in tuberculous organs, and with the help of tuberculin the occurrence of a specific antibody in the blood, namely, anti-tuberculin.

From these data they grounded a new theory of the action of tuberculin, which has given an impulse to numerous investigations in the last few years.

As this tuberculosis experiment had shown the possibility of proving the presence of antigen in diseased organs, and especially the use of these organ extracts as antigen, an advance could be made to employ the fixation of complement method for the diagnosis of diseases, where no cultivable causal micro-organism existed; because in this instance, in place of the bacteria extract, an organ extract was proved, in which the presence of antigen could be reasonably supposed.

Working on these lines Wassermann, Neisser and Brück⁽⁷¹⁾ introduced the reaction for the serum diagnosis of syphilis, and at the beginning of 1906 published their results in the case of syphilitic monkeys, soon followed by those relating to the human species.

This reaction has been greatly elaborated in the last few years, and has caused more interest than any other previous biological reaction.

The complicated experimental appointments, the great exactness and rudimentary biological knowledge that the reaction presupposes, make it appear natural that a great number of attempts were made to simplify the serum diagnosis of syphilis. But none of these can replace or even approach the reaction of the fixation of complement.

This difficulty in the performance of the operation, brought with it the result, that its undertaking remained confined to central institutions in the majority of cases, where the necessary apparatus materials and last though not least biologically trained and efficient staff were available.

It must remain so until the avoidance of numerous sources of error which so far only the highly trained can adjudicate, is obviated. From this goal we are still far removed.

On this ground the serum diagnosis of syphilis does not belong to the general practitioner. The method is too complicated and the results, from which at times the whole happiness or woe of entire families depend, are too weighty to be placed outside the control of large clinics, hospitals or central institutes which are able to undertake responsibility.

In Vienna first of all the importance of this matter was fully recognised, and a central institute was founded for the purpose of carrying out this serum diagnosis.

The next central institute was founded at Breslau and now there are such places scattered over every country.

The carrying out of the reaction on a satisfactory basis demands the following conditions:-

- i. The examination of at least 20 sera at one time.
- ii. Examination in the active condition.
- iii. Examination in the inactive condition.
- iv. The employment of several extracts.
- v. If need be examination after Wechselmann.
- vi. If necessary, repeated examination of the same serum.

In addition must be mentioned the important preliminary reaction before the performance of the actual reaction, namely, the titration of the complement and amboceptor.

This work demands 4 - 5 hours labour daily from a skilled investigator. We can neither expect nor demand such an occupation from a general practitioner.

When the work is not carried out properly there is no wonder if the Wassermann reaction falls into discredit. This happened a few years ago in Berlin, where individual specialists carried out their own Wassermanns, untold confusion being the result.

In London now it is the practice of certain specialists to do their own reactions, having perhaps from 5 to 10 sera to examine at a time.

In my opinion such procedure is not only unscientific and unreliable, but borders on the criminal, for such results are in many cases not worth the paper they are written on.

NATURE OF THE SYPHILIS REACTION.

The reaction is caused by two components.

i. Specific component.

A specific amboceptor is formed against an unknown substance produced by the micro-organism of syphilis. Experimental evidence indicates that this specific substance plays a certain part in the reaction, but in its practical bearing, as affecting the reaction, its role, is insignificant.

ii. Non-specific components.

In syphilis, substances, probably albumen-lipoid combinations, pass from the organs into the blood stream.

When these are mixed with an identical or closely related substance of an organ extract they show an absorption of complement depending on physico-chemical antecedents.

The assertion that an auto-antibody formation ensues cannot be maintained.

The fixation of complement therefore rests only to a partial extent on an immunity reaction; the

most important part of it is of a purely physico-chemical nature, consummated between two substances either absolutely identical or almost so.

VALUE OF THE WASSERMANN REACTION IN PRACTICE.

With such means of diagnosis at our disposal, (and possessing excellent means for treatment) the number of cases of Syphilis should steadily diminish.

At the Breslau Klinik it was a routine practice to do a Wassermann reaction in every case admitted to the hospital. No doubt it was often quite unnecessary, but now and then a case of syphilis was unexpectedly brought to light and suitable treatment adopted. Though such a course is not possible in private practice, in hospitals where a great number of blood examinations are carried out, these additional cases are quite valuable to act as controls.

Whenever suspicion is entertained that some lesion, that existed years before perhaps, might have been syphilitic, it is worth while performing a Wassermann.

We are sometimes set face to face with the question - Is the patient really cured of the disease or is it still present in a latent condition?

In the majority of cases a definite opinion can now be given, aided by the serum diagnosis.

The positive result is a sure indication of the presence of the Spirochaeta pallida somewhere in the body.

Consequently we can now treat cases whom we formerly did not treat through failure to recognise the disease, or whom we did not continue to treat believing them to be cured, or in whom no idea of an infection had existed.

The serum diagnosis is therefore indispensable when an opinion has to be given in any case of syphilis which presents no manifest symptoms. It alone can help us to decide the difficult question as to how long one must continue treatment in order to free the individual from the virus that is harboured in the infected system.

Hence we must urgently demanded that any individual of whom even the slightest suspicion is entertained that he has been infected from a known or unknown source, must have his serum examined so as to disclose these hidden and latent cases. It is only in this way that we can hope to cure them and guard them against the much dreaded para-syphilitic complications.

THE EXPLANATION OF THE NEGATIVE REACTION. is not so simple. It is quite false to state that a negative reaction carries no meaning with it. A single negative reaction is valuable in old cases of Syphilis, and in fresher cases it is at any rate a valuable indication of a favourable advance towards the end we have in view namely the eradication of the disease.

A provocative injection of salvarsan in suspicious cases may cause a change in the Wassermann reaction from negative to positive. This is sometimes a very useful procedure.

VALUE IN EARLY STAGES.

It may be of great assistance but we must not forget that even in cases of undoubted infection a certain time must elapse before the test can be of value. On an average this period is six weeks. To this rule there are, of course, exceptions. In some rare cases the Wassermann is positive before the appearance of a diagnostic primary sore.

It is interesting to note that in Neisser's experiments on apes the Wasserman became positive within 3 or 4 weeks of infection, before the appearance of a diagnostic primary sore.

The positive reaction is a sign of the generalisation of the virus of syphilis throughout the body.

During the secondary period of untreated syphilis at the Breslau Klinik results showed that 94.1% of cases gave a positive reaction. Since the introduction of Margarete Stern's⁽⁷²⁾ modification there has not been a single case of secondary syphilis which did not give a positive reaction.

INTERTIARY SYPHILIS.

The Wassermann proves positive in from 70 to 80% of cases.

The differential diagnosis between it and Lupus, Sporotrichosis and scrofuloderma, and occasionally Psoriasis and a few other skin affections may present real difficulty.

There were two well known cases at the Breslau hospital which had been treated for years as lupus and which proved to be really cases of syphilis. They were recognised by the Wassermann reaction and successfully treated, but not before the features had been horribly destroyed in both cases.

The history of the case may help to elucidate the mystery but sometimes this is of no great value.

The presence of old tertiary sears may help. One can try the effect of Iodide in large doses.

The frequency of the negative reaction is probably due to the diminished amount of syphilitic virus in these tertiary cases, compared with the secondary period. There are certain resemblances between the tertiary period and the earliest stage

before the appearance of secondary signs. In both cases we are dealing with a more or less circumscribed herd of spirochaetes.

Bering⁽⁷³⁾ found that in polysymptomatic cases of tertiary disease the positive reaction appeared in 93% of cases, whilst in mono-symptomatic cases it was only in 37% of the cases.

Cases of leucoplakia linguae have been shown to be related to Syphilis even more frequently than was believed. But we can not say definitely that all cases of leucoplakia are of syphilitic origin.

LATENT SYPHILIS.

Under this name are included all cases whose exanthemata have disappeared and who clinically show nothing more than a polyscleradenitis, or perhaps a leucoderma, as well as those who perhaps 40 years ago suffered from syphilis.

In other words the man who has had syphilis remains in the eyes of the medical man a latent syphilitic all his life.

The division into early and late periods can be best made by considering all cases up to two years after infection as early latent cases, for the majority of tertiary lesions appear during the third year after infection.

In general the positive reaction appears in from 50 to 60% of all latent cases of Syphilis.

PART IV.

TREATMENT.

The modern treatment of Syphilis is based upon a series of scientific discoveries in the spheres of etiology diagnosis, experimental pathology and therapeutics.

- i. The discovery of the Spirochaeta pallida by Schandinn.
- ii. The discovery of Metschnikoff and Roux regarding the susceptibility of apes to inoculation, as well as the discovery by Bertarelli that rabbits are likewise susceptible.
- iii. The researches of Neisser and his assistants in Java in the region of experimental therapeutics.
- iv. The serum method of diagnosis known as the Wassermann reaction.
- v. Ehrlich's⁽⁷⁴⁾ new therapeutic researches resulting in the discovery of arsenic preparations notably Arsenophenylglycin, Dioxydiamido-Arsenobenzol and Neo-salvarsan, which are of great value in treating syphilis.

Some very important facts have been disclosed by these researches.

Neisser has clearly demonstrated that every case of syphilis must be treated in a thorough and

energetic manner, for without a specific treatment an absolute cure of syphilis does not take place. The cases which become well without treatment are so very rare that we can never hold out that hope to our patients.

He further showed through his experiments on apes that the whole of the former teaching of the immunity said to follow an attack of syphilis is completely untenable and without foundation.

The fact of the matter is that formerly the majority of cases remained uncured, and as long as there was still syphilis anywhere in the body a protection existed against further infection.

As long as the virus of syphilis remains in the body there exists a nearly complete resistance to reinfection.

Super-infection is possible, although rare.

Neisser's researches have also established the following result that there neither exists nor probably can exist an artificially active or passive immunity of any sort.

Since a serum therapy is practically out of the question we have to turn our attention to a chemotherapy.

Mercury has been employed for more than four centuries to combat the ravages of syphilis.

Now, thanks to the genius of Paul Ehrlich, we possess powerful arsenic preparations which have proved themselves of inestimable value.

He it was who first pointed out how the saturated quinquevalent arsenic combinations differed from the unsaturated trivalents in their inherent principles, the former being of much less therapeutic value.

Ehrlich was the first to perceive what consequences might result through combining quite different chemical groups with the arsenic triad.

From his laboratory came first arsenophenylglycin and finally Salvarsan and Neo-salvarsan.

I was at Breslau when the first samples of Salvarsan were sent to Prof. Neisser for trial and investigation, and was able to follow the results during the three years I was there.

At first it seemed so wonderful that all thought that Ehrlich had been right in saying that Syphilis would be eradicated "mit einem Schlage".

Experience has proved this statement to be too optimistic for the generality of cases, although I have seen individual early cases which have been apparently cured by a course of two or three intravenous injections. In any case the Wassermann reaction has remained constantly negative.

Thus we now possess two powerful remedies in Mercury and Arsenic.

Of the Arsenic preparations I shall confine my attention to Salvarsan, the most powerful and effective of them all

SALVARSAN.

The value of salvarsan in our therapy is inestimable if only as a substitute for Mercury in such cases in which Mercury is either contra-indicated, useless, or dare not be administered, namely:-

- i. Cases of idiosyncrasy with regard to mercury.
- ii. Cases which have apparently become resistant to mercury.
- iii. Cases of hypersensitiveness of the intestinal tract and kidneys.
- iv. Cases where organs important to life are involved where speedy and effective action is desired.
- v. Stomatitis can be avoided.

NATURE AND MANNER OF ITS ACTION.

Salvarsan has a direct spirillocide action and probably too it causes an increase in the production of normal antibodies.

Further, unless we ascribe a direct anti-toxic effect to salvarsan it is difficult to explain satisfactorily the extraordinarily rapid release from pain and other distressing symptoms so frequently brought about in but a few hours after injection.

Finally the rapidity with which ulcerating and spreading processes heal under salvarsan suggests a definite organotrope action.

I have seen such lesions clear up and heal in a manner little short of the miraculous.

I shall give one instance of the power of salvarsan.

A friend of mine suffering from tertiary syphilis especially affecting his turbinate and nasal bones, as well as the palate, was under various treatments with Mercury, in all forms, and Iodides in London and Aachen, finally leaving the latter place after three 6 week cures apparently free from disease.

Within six months he had a serious relapse, this time his upper lip and the left ala nasi were affected. His medical man did not believe in Salvarsan, then practically in its infancy, but as the thing gradually got worse and threatened absolute destruction of the area involved, he at last agreed to try Salvarsan, on my advice.

He received two injections each being 0.6gm., the first one intramuscular, and the second one intravenous.

Within a few days of the second injection the lesion had healed and since then there has been no sign of further disease.

His spirochaetes had evidently become resistant to mercury.

Rapidity of action is sometimes of supreme importance. For example in some cases of malignant syphilis with its accompanying ulcerating lesions, as well as in cerebral syphilis and ulcerating processes threatening the nose, lips, palate, genital organs, &c., cerebral syphilis (not advanced) reacts very remarkably. I remember certain patients who suffered excruciating agony from headache, and fearful prostration, who on the morning after a single injection presented smiling and happy faces freed from pain and all distress.

CONTRA-INDICATIONS AND DANGERS OF SALVARSAN.

The only contra-indications are severe cachexias, far advanced cases of spinal and cerebral syphilis (not early cases) and especially where there is a strong suspicion of myocardial disease. There has been considerable controversy concerning the damage to sensory nerves ascribed by some observers to the direct toxic action of salvarsan.

These nerve lesions have undoubtedly increased in number since it was introduced. Perhaps it is a neuritis analagous to a local inflammatory reaction set up in a nerve already damaged by syphilis.

My idea of the thing is that they are genuine relapses of syphilis due to the stimulation of a nest of spirochaetes localised in the nerve itself, or its immediate neighbourhood. It may be due to

an inflammatory periostitis of the bony canal through which the nerve passes, producing pressure paralysis. At any rate energetic administration of anti-syphilitic remedies of mercury, as well as salvarsan, usually succeeds in curing these most unpleasant manifestations. When I was in Breslau we met with comparatively few of these nerve lesions. My explanation is, that from the beginning Neisser employed large doses of salvarsan, and as soon as the experimental stage was over always administered moderate to large courses of mercury in combination with salvarsan. This vigorous employment of the chronic system of treatment has evidently either prevented the localisation of spirochaetes in the nerves, or has rapidly eradicated them.

Deaths have occurred after administration of salvarsan, directly attributable to the injection.

In December 1912 Marschalko and Veszprémi⁽⁷⁵⁾ published an interesting paper relating to this subject.

They conducted a series of experiments to try and find out if the reaction so often produced by salvarsan injected intravenously, were due to a toxic action of salvarsan itself or due to the contamination of the saline solution used to administer the salvarsan.

It was held by many that the dead bodies of bacteria contained proteid substances which acted in a toxic manner and produced the unpleasant reactions.

The experiments of these investigators seem to demonstrate clearly that salvarsan itself is to blame.

The substitution of sterilized distilled water has not eliminated the intoxications. They proved that the so called "Wasserfehler" plays an insignificant role, if any at all.

The deaths from encephalitis which have occurred are directly attributable to the toxic influence of salvarsan,

Their deduction is that salvarsan has been used too indiscriminately with regard to its dosage and they recommend repeated small doses administered at suitable intervals. If this is done the danger to life will be very greatly diminished without reducing the power of salvarsan to effect a cure.

Wechselmann does not agree with these statements.

Wechselmann(76) of the Rudolf Virchow-Krankenhans at Berlin has had an enormous amount of experience with salvarsan infusions. He has not had one single death in more than 12,000 cases that could be attributed to the toxic effects of salvarsan.

He ascribes his success to his development of a careful technique, and since his latest improvements has injected thousands of patients without having any dangerously unpleasant experiences. The fact that sometimes as many as fifty patients are treated daily speaks eloquently of the safety of his method, for it would be almost impossible to inject so many patients if there were delays and interruptions caused by any grave accidents.

He regards the bacterial contents of saline solution as the main cause of strong reactions and the accompanying somewhat alarming sequence of symptoms, in the shape of cyanosis, rigors, high temperatures, as much as 104° Fahr. vomiting, diarrhoea, fearful headache and pains in the back, which although they may not last more than a few hours, sometimes cause great anxiety and frequently necessitate the administration of camphor oil, &c.

Certainly after the introduction of his technique at Breslau there was a marked falling off in the occurrence of strong reactions and the practice grew considerably to treat more and more patients in the outpatient department. The injections were

given from 9 a.m. onwards. As a rule patients remained in the hospital until the afternoon and went home from 3 to 6 hours after the infusion.

This procedure was a great success and saved a great deal of time and money, for previously patients always spent the night in the wards, sleeping on couches and occupying beds that could ill be spared.

With these preliminary remarks I shall now proceed to consider the means at our disposal for treating syphilis, especially emphasising the value of a combination therapy comprising intravenous infusion of salvarsan and intramuscular injection of mercury.

Local treatment should be carried out in an efficient and thorough manner.

Where practicable excise the primary sore otherwise cauterise it. Then apply calomel, iodoform, noviform (an odourless substitute for iodoform) black wash, &c.

Ulcerations of the fauces can be touched with successive applications of 10% Silver nitrate and 20% Chromic acid at each sitting. This combination is very effective.

A gargle containing Pot. chlorate and Carbolic acid or Tinct. Myrrh &c. should be prescribed.

GENERAL TREATMENT.

As soon as a diagnosis is established commence treatment at once. Not a day should be lost. The sooner we commence the greater will be the chances of success. It is always advisable to explain the contagious nature of the disease for some people are most surprisingly ignorant on this point.

Advise a healthy hygienic manner of living - regular hours; regular meals; no smoking; no spirits, claret or dark lager beer if anything and only in moderation; suitable diet, with avoidance of sharp condiments, strong coffee &c; careful attention to the teeth which are to be brushed after each meal using a tooth paste such as Pebecol or Saluferin; a visit to a dentist is desirable; assiduous gargling using a teaspoonful of Hydrogen Peroxide to a glass of water, several times daily; finally no late hours.

The mental as well as the physical condition should be treated. Encouragement and kindness will often raise a patients spirits from the region of zero, and by the creating of a brighter outlook the effect of treatment tends to be heightened.

I MERCURY can be administered in several ways)

- i. By the mouth.
- ii. By inunction.
- iii. By injection.
- iv. By vapour baths
- v. By mercolint bibs.

Each and all succeed in getting mercury into the system, but injection is the method of choice for the following adequate reasons.

It is on the whole the most scientific and efficacious method. You know exactly how much the patient is getting. It is clean, convenient and does not upset the stomach.

II. ARSENIC PREPARATIONS.

- a. Arsenophenylglycin Ehrlichs 418.
- b. Alt. Salvarsan Ehrlichs 606.
- c. Neo-salvarsan.

Atoxyl and Arsacetin are too dangerous.

III. ANTIMONY PREPARATIONS.

Various attempts have been made to include antimony in our list of therapeutic measures.

I have seen intravenous infusions made with it, but so far the right combination has not been discovered. Results, however, are encouraging and Neisser thinks that before long we shall have this extra weapon to support us.

IV. IODIDES.

COMBINATION THERAPY.

In my mind there is no question as to which drug we are to choose, unless in certain special cases, but merely, what is the best way of administering both mercury and arsenic. In any case we are giving the patient the best chance by attacking

the enemy on two flanks. We have the acute action of salvarsan injected intravenously as well as the chronic action of mercury and perhaps arsenic as well, by the formation of depots in the system which subject the organismus to the constant influence of our remedies. Salvarsan is distinctly superior to mercury as a rapid destroyer of spirochaetes and in consequence is especially indicated when we want to apply the abortive method of treatment. The value of this abortive method is too little appreciated by many medical men.

CHOICE OF REMEDIES.

INTRAMUSCULAR MERCURY INJECTION.

There are a great number of preparations to choose from. I can thoroughly recommend the following preparations.

A. ASUROL, a double soluble salt of mercury salicylate and acid sodium amidsoxyisobutter, containing 40.3% of Hg.

Its advantages are that large single doses can be given; its action is rapid; it is comparatively painless; it does not form a combination with albumen and consequently no infiltrations appear at the site of injection either of a hard or inflammatory nature; elimination through the bowel more than the kidneys. 1ccm of a 10% Asurol contains 0.04 Hg.

B. MERCURY SALICYLATE is the mildest of the insoluble mercury salts, in great favour in Berlin, and a very useful preparation indeed.

C. OLEUM CINEREUM is more powerful than mercury salicylate, and is the one chosen by Neisser on account of its efficacy.

Dr. Siegfried Jablonski, Scheitniger strasse, Breslau, has succeeded in obtaining oleum cinereum preparation which has removed all the harsh judgements so frequently urged against it. He produced a 40% oleum cinereum (mercinol) which has excellent features. It can be injected in small bulk containing a high percentage of very finely divided mercury. It rarely causes infiltrations of any consequence, is painless and well borne, apart from a certain amount of stiffness which accompanies most intra-gluteal injections. Supplied with the preparations of Jablonski is a special Barthèlemy syringe divided into 14 parts. Each division contains 0.01 gm. Hg, when this 40% Mercinol is employed. One can administer the required dose with great exactitude. Personally I have been very satisfied with the method. I am sending some samples, and a syringe with platino-iridium needle for trial purposes if desired. It is not advisable to boil the syringe and needles, careful attention and preservation in sterilised

parafinum liquidum is quite sufficient.

D. CALOMEL is still more powerful than oleum cinereum. Its action is speedy and powerful indicated when you want to get the patient under the influence of mercury as soon as possible. It is not suitable for prolonged routine administration.

INTRA-VEINUS INJECTION OF ARSENIC COMPOUNDS.

a. SALVARSAN, 606, is the one I choose. Despite all its disadvantages it has proved itself the most effective of all the arsenic preparations. It has 40.9% of As.

b. NEO-SALVARSAN is said to be less toxic and equally effective, also capable of administration in higher doses with safety.

Experience at Breslau and elsewhere, after the trials were somewhat extended, shows that it is not as powerful as Salvarsan, and when given in large doses is just as liable to cause alarming symptoms.

It has the great advantage of being alkaline and easily prepared for infusions. It has only to be dissolved in distilled water, cooled to the room temperature and injected. It is advisable to precede and follow its injection by administration of 0.5% saline solution.

Intramuscular injection of neo-salvarsan is said to be most satisfactory. Infiltrations hard

and inflammatory leading to subsequent necrosis are said to be absent.

For purposes of injection 0.45 grm. are dissolved in 7.5 ccm of sterilised distilled water. However, Neisser, Hoffmann and others regard it as inferior to the old salvarsan.

c. ARSTENOPHENYLGLYCIN, also known as Spirarsyl, contains 33.8% of As.

It is a very unstable compound and easily decomposes.

Neisser sometimes injects it intramuscularly into the gluteal region with good results, but not as a routine procedure. It is perfectly safe. It is a bright yellow powder readily soluble in water, easily oxidised by contact with air and preserved in small vacuum phials.

It was prepared at Breslau in such a manner that $7\frac{1}{2}$ ccm of the injection solution contained 0.75 grm of the drug.

Owing to the rather painful nature of the process 1ccm of a 5% novocain nitric. solution was mixed with it. At intervals of a few days a series of four doses was given commencing with 0.1gm and going on to 0.5 then 0.75 and again 0.75 grm.

TECHNIQUE OF THE SALVARSAN INFUSION.

I now come to the important question of preparing the solution for intravenous injection and the technique adopted.

We propose to inject a substance, far from being indifferent, into the blood stream, consequently we should take precautions and perform the operation something in the spirit with which a surgeon prepares to do a laparotomy.

Strictest attention to the minutes details is necessary to get the proper result.

1. Glass retorts and ordinary measuring cylinders, a glass funnel, a pipette with rubber ball attachment are washed in cold soda solution using a brush.

Then after rinsing in freshly distilled water place them in a dry steriliser whose opening is underneath.

Dissolve 9grm of Natrium chlorat.puriss (Merck or some other reliable source) in 1 litre of freshly distilled water.

2. Filtration of the 0.9 per cent saline solution through a hard filter and boil vigorously for half an hour. Add some filtered aqua destillata that has been boiled half an hour to make up for what is lost by the boiling.

Cool in an ice chest. Warm up to 36°C and inject as soon as possible.

At the same time 4 volume per cent of sodium hydrate is boiled in a water-bath.

3. Add 10-20_{ccm} of hot saline solution to a retort capable of holding 300_{ccm}.

The Salvarsan powder is sprinkled over its surface carefully so that it falls like dust and not in lumps. It dissolves very quickly under these circumstances.

4. Now add the 4 volume per cent Sodium hydrate until the cloudiness begins to disappear.

Then carefully drop by drop add more sodium hydrate until the solution becomes clear and transparent. Vigorous shaking and heating over a Bunsen flame aids the solution and prevents an excessive addition of sodium hydrate.

5. Filter in a careful manner through a funnel whose opening is closed with well boiled damp cottonwool until not a trace of anything is seen in the salvarsan solution.

Add cool saline solution in the proportion of at least 0.1 Salvarsan to 60_{ccm}.

6. The patients arm is shaved, washed with soap(Duncan and Flockhart's aetherseal anti-septic soap is excellent), sublimate solution and then cover with a dressing of gauze or mull soaked in 50% spirit. Disinfection with Tinct. Iodine makes the needle blunt.

7. Allow the arm to hang suspended with the fist firmly clenched. After a little time apply a piece of Bier's bandage to constrict the arm, but not too tightly, and fasten the bandage with artery forceps.

Place the arm back on the table and tap the chosen vein with a sterile percussion hammer.

Choose smaller veins than the prominent cubital veins in the flexure of the elbow. The veins running over the styloid process of the radius and from the thumb over the wrist are excellent, possessing thick walls and well fixed underneath.

So if possible use the veins of the forearm for if a thrombosis unfortunately occurs it is not such a serious matter, and further the superficial position of them allows you to observe a commencing infiltration of the tissues with great ease.

Even if filtration does result it is not so annoying as one in the elbow flexure.

8. A bayonet shaped needle lies very well in the vein. The blood which rushes back along the rubber tube must not have air bubbles in front of it as seen through the glass window. (The injection apparatus will shortly be described).

If there is air present let the blood pass back into the little reservoir over the nickel ball. Here it mounts up to the stopcock and is out of harms way.

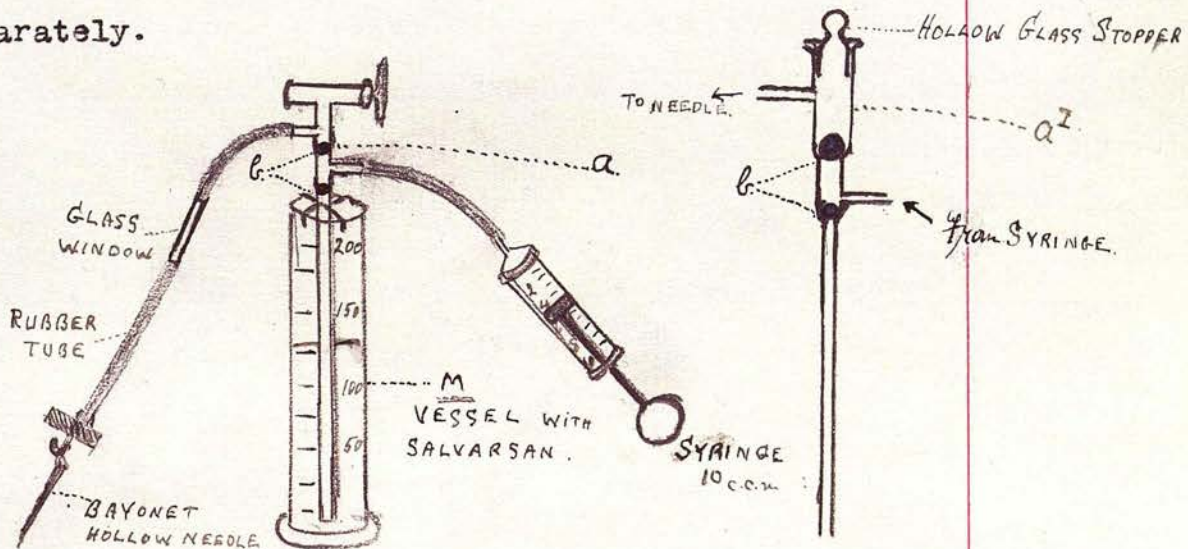
9. It is not necessary to inject saline solution before and after the injection, but this can be done.

10. At the slightest indication of pain you can tell whether the needle is in the lumen of the vein by opening the stopcock and gently manipulating the rubber tube.

11. The needle must not be fixed in the vein.

APPARATUS.

Wechselmann's "Kugelventilapparat"(77) is a very convenient and highly satisfactory one. It is made of a durable hard glass. The whole thing is sterilizable; remember to sterilize the nickel balls separately.



The essential apparatus consists of a glass tube (a) in which two conical "valves" are ground (see section a¹).

These valves are closed by two nickel balls of different sizes (b).

A branch above the lower ball leads to a syringe of 10_{ccm} capacity, and another branch leads to the needle which is connected with the main tube by a short rubber tube in which a glass tube is interposed to act as a window (w).

Fill up the apparatus with saline solution by aspirating with the syringe. The air pressure keeps it full and no more air can get in. Any air bubbles can be easily got rid of.

Then place the apparatus in a suitable vessel, such as a measure cylinder of 200_{ccm} capacity (m) which holds the salvarsan solution.

Introduce the hallow needle into a vein and you can now proceed automatically to aspirate salvarsan solution into the syringe whereat the lower valve opens, and then inject it into the vein whereat the lower valve closes and the upper one opens. The valves close again automatically through the sheer weight of the nickel balls. It is almost impossible to introduce air into the vein and even when you have unskilfully aspirated some air this collects in the syringe and even if you force it out of the

syringe it rises to the uppermost part of the glass tube and floats in the hollow glass stopper. Further, air bubbles can be seen in the glass window.

The precision and ease in which the apparatus works is highly satisfactory. It can be operated by one man without any assistant.

METHOD OF COMBINATION TREATMENT.

Thoroughly test the urine especially for albumen. A trace of albumen is not a necessary contra-indication for the use of mercury. It frequently disappears during administration. If it unduly increases of course stop the Hg. and if unhappily infiltrations occur at the site of injection the gluteal muscles being chosen, stop the oleum cinereum and proceed with mercury salicylate, or stop mercury altogether for several days, according to the condition present

1. Begin the cure with two Asurol injections.

1st injection,

$\frac{1}{2}$ ccm of a 10% Asurol solution = 0.02 Hg.

Two days later

2nd injection.

1ccm of a 10% Asurol solution = 0.04 Hg.

Total Hg. = 0.06

On the 5th day 1st infusion

A trial dose of salvarsan (0.2 - 0.3) to

minimise the excitatory reaction. If there is any suspicion of meningeal symptoms examine fluid from lumbar puncture.

On the 7th day give the 1st oleum cinereum injection,

3rd injection ^{half} Barthélemy syringe = 0.07 Hg.

Total Hg. = 0.13

On the 9th day give the second salvarsan infusion.

2nd infusion. Dose (0.4 - 0.6)

On the 12th day give oleum cinereum.

4th injection ^{half} Barthélemy syringe = 0.07 Hg.

Total Hg. = 0.20

On the 14th day give the 3rd salvarsan infusion

3rd infusion Dose (0.3 - 0.6)

On the 19th day give the ~~3rd~~ oleum cinereum

5th injection 1 whole Barthélemy syringe = 0.14 Hg.

Total Hg. = 0.34

You can either give two half Barthélemy injections, or one whole one each 7 or 8 days until a total amount of 0.8 - 0.9 Hg is given in a single course.

Some people repeat the salvarsan injections 4 to 6 times at intervals of 3 to 5 days.

In some cases this is advisable whilst in others three infusions are sufficient for one course.

On the 21st day give the fourth salvarsan infusion.

4th infusion Dose (0.3 - 0.6)

At the beginning and end of the salvarsan infusions examine according to Wassermann.

If the reaction is negative, examine again four weeks later.

Eight months after the lasting negative reaction first appeared, give a provocative salvarsan infusion (0.4.) If it proves negative repeat the process six months later. If after two provocative reactions the Wassermann remains negative, examine the patient thoroughly from a clinical standpoint.

Further, examine the fluid from lumbar puncture. The condition of the cerebro-spinal fluid in syphilis is fairly characteristic regarding its cell elements. There is a marked increase in the number of small lymphocytes with a few large lymphocytes with lobed nuclei. Practically the only other diseases which produce a similar picture are meningeal abscess, tuberculous meningitis, the irritation of tumours, abscesses and foreign bodies.

If the Wassermann remains positive a second course of salvarsan infusions should be at once given, followed by further Wassermann examination.

Three months after the conclusion of the first mercury course with positive reaction repeat the procedure combined with salvarsan.

Hoffmann gives Hg. salicyl. in the form of a 10% emulsion in doses of 1_{ccm} every 4 or 5 days

until 15 in all are given, and at the same time gives 4 to 6 Salvarsan infusions. He also favours inunction or alternates inunction with Hg. salicyl injections, giving either a course of 40 rubbings with 4 - 5 grm daily doses or merely several inunctions.

INJECTION OF SALVARSAN IN THE CASE OF INFANTS.

Use the same fluid as for intravenous injection which contains 0.1 salvarsan to 60_{ccm} saline solution. Inject 5 - 10_{ccm} of this solution subcutaneously.

The milk of a mother who has been treated with salvarsan seems to have a beneficial effect on the child she is nursing.

IODIDES.

That Iodides are beneficial in removing the products of syphilitic activity has been long recognised.

They have been administered with success in tertiary syphilis and even in secondary stages where there is a widespread distribution of papular syphilides.

There was no ground for believing that iodides had any power to destroy the micro-organismal cause itself.

Neisser conducted experiments which showed that in syphilis of monkeys Iodides possess a healing power as well. Thirty syphilitic animals were

treated with Iodides alone in large doses. Twelve of the animals were cured, proved by reinoculation in two cases and negative results on inoculating with organs in ten cases.

This is interesting but is no proof that Iodides act in a similar manner in ^{the} human species.

However, whenever there are tertiary lesions it is advisable to administer iodides.

Wherever there are shut up herds of spirochaetes it is quite reasonable to imagine that Iodides can break down these and render the spirochaetes accessible to the remedy administered.

I always administer it in the following combination. The patient tolerates it very well.

R/ Potass. Iodid.

Sod. Iodid. ¹aa 10,0 grm.

Antipyrin 5,0 grm.

Aq. dest. ad 300,0

Sig. A tablespoonful three times daily.

The patient gets about 45 grains daily.

COMMENTARY AND CONCLUSIONS.

This short review can do no more than outline the vast progress that has been made, and suggest the untold labours and researches that have been carried out by hundreds of investigators.

The source of my information is mainly German in origin.

In this question the German Scientists have borne the brunt of the battle of late years, with the able co-operation of various distinguished French and American colleagues.

British resources are not sufficiently organised and the arrangements for research work on a large scale are are totally inadequate.

In the eyes of the general public Syphilis is a most unsavoury subject. This natural distaste is accompanied by comparative ignorance, and education in certain directions would be eminently useful.

Its importance as a constant source of danger to society should be spread amongst the people. Medical men need all the help they can get in order to combat the ravages of this human scourge.

Why should we not in Britain adopt a similar course to the Germans and distribute literature and deliver public lectures?

In Germany the "Gesellschaft zur Bekämpfung der Geschlechtskrankheiten does splendid educative work.

Why should not the laity know, for instance, of the extreme importance of early and thorough treatment of Syphilis?

The value of the abortive method of treatment is too little appreciated even by many medical men. Now that we possess Salvarsan, if we could only get at these very early cases what a wonderful reduction would be made in the aggregate number of syphilitic individuals! What misery could be obviated, and what great numbers of valuable lives could be saved for the nation. We shall have to face the question of Syphilis just as we are now at last endeavouring to fight tuberculosis.

Away with false sentiment!

I am a firm believer in Prof. Neisser's method of treating Syphilis. He is one of the most rigorous therapeutists in Europe. Energy and thoroughness are characteristic of the man as well as his treatment.

After all it doesn't matter if you give a man a little more inconvenience if you are increasing the chances of curing him.

A man who has had Syphilis should never forget to have his system tested even after a two or three years treatment.

A Syphilitic individual can be regarded as cured when he passes the necessary clinical and biological tests - when after a thorough clinical examination

he is free from all symptoms of the skin, mucous membranes and internal organs. When his serum is proved healthy by Wassermann reactions; when his cerebro-spinal fluid shows no abnormality. He should have his blood examined at yearly intervals for several years. This may not be absolutely necessary but it certainly seems a safe procedure.

On the appearance of any ~~nervous~~ symptoms, even if the Wassermann is negative, the cerebro-spinal fluid should be examined from Lumbar puncture.

No doubt Ehrlich's sterilisatio magna is under certain conditions attainable.

The great number of re-infections that have occurred since Salvarsan is a proof of this.

The identity of the *Spirochaeta pallida* is now firmly established, but the question as to its divisions, and reproduction is not yet solved.

Probably McDonagh is on the right lines, but his observations require to be authoritatively established before we can accept them. He has seen the whole cycle of sexual reproductions, as well as an asexual reproduction.

I would like to emphasise the value of the microscope in examining early suspicious primary sores. In the dark field examination patience and thoroughness are the watchwords.

I have often found genuine *Spirochaeta pallida* in discarded preparations regarded as negative by

my colleagues in Breslau, because I was especially keen on the subject and searched more diligently.

We must not forget that mercury is still a powerful anti-syphilitic remedy, and in the adoration of salvarsan allow it to fall into disuse. It ought to enjoy the honour of full partnership and not be relegated to the position of an inferior subordinate.

We can however now slightly reduce the total amount given in a prescribed course, and thereby minimise the dangers that are inseparably associated with its proper and energetic administration.

The weight of evidence shows that the *Treponema pallidum*, if not a protozoon, has at any rate close family biological relationship with it.

Trypanosomiasis calls forth quite analagous lesions in the central nervous system.

Dohi and Hidaka (Archiv. f. Derm. u. Syph. cxiv B. 2 H. 1912. December) found in a series of interesting experiments, that spirochaetes have biological relationship to the Protozoa, but between Spir. and Bacteria as demonstrated by the reactions of immunity there was no relationship.

Profeta's law of inherited immunity is untenable. There is opposition to it on every hand. The so-called inherited immunity is no doubt due to the presence of latent congenital syphilis, and before it can be accepted as a fact this latent condition has to be disproved.

The question of paternal syphilis is full of difficulties. Proofs are not easily established, but there seems good reason to believe that a child can be infected a patre without the mother acquiring syphilis.

The Wassermann reaction has established itself on a firm basis and is indispensable.

In addition the microscopic examination of the cerebro-spinal fluid is claiming more and more attention as a valuable adjunct to our means of diagnosis and control of treatment, seeing that it affords us valuable information of the condition of the central nervous system.

Para-syphilitic complications must decrease in number if the modern treatment of earlier cases is rationally and properly carried out.

Arsenic has been found in the cerebro-spinal fluid. Salvarsan is especially efficacious in cases of cerebral syphilis and malignant syphilis. With regard to Tabes dorsalis the results have not been very satisfactory.

Noguchi has found sp. pallida in sections from the brain in general paralysis, in a high percentage of cases examined.

The majority, if not all are due to syphilis infection.

Some people might regard the elaborate precautions taken in preparing and injecting Salvarsan as superfluous.

I am quite convinced that this care is not a waste of time and energy.

From the clinical standpoint at any rate, it has practically caused the disappearance of strong reactions and the associated dangers to life. There have been cases of death which seem to be directly attributable to salvarsan but they are in any case a minimal percentage of cases injected and do not deter us from continuing to inject a dose as high as (0.6 gm).

In the milk of a mother who is under the influence of salvarsan, there are present either anti-bodies or traces of arsenic which have a favourable effect on the syphilis of the suckling child. However the child should be further treated with mercury inunction and subcutaneous injection of salvarsan, giving a dose of 5 to 8 milligrams per kilogram of body weight.

In the army and navy in Germany as prophylactic measures, either the Neisser-Siebert or Metschnikoff disinfecting ointment are largely employed, thereby greatly lessening the number of infections.

They consist of:-

Metschnikoff's 33% calomel ointment.

Neisser -Siebert ointment.

R/SSublimite	0.3
Saline Sol.	1.0
Tragacanth.	2.0
Amylum	4.0
Gellatin.	0.7
Alcohol.	25.0
Glycerin.	17.0
Aqua dest.	ad 100.0

The names of Ehrlich, Schaudinn, Neisser, Wassermann, Bruck, Hoffmann, Metschnikoff, Roux, Bordet and Gengou must be honoured for the great labours and the far-reaching results their discoveries have led to in the diagnosis and treatment of Syphilis.

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